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INDEX NUMBER

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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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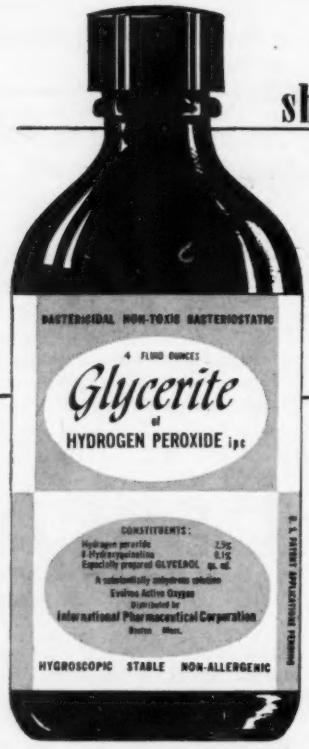

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everted or end-to-end

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Stomach - Intestines

serosa-to-serosa or end-to-end

mucosa pouting through

Fibrin deposited at red arrows (↓) makes anastomosis gas and water tight

SUTUREGRAM NUMBER FIVE (CONTINUED)

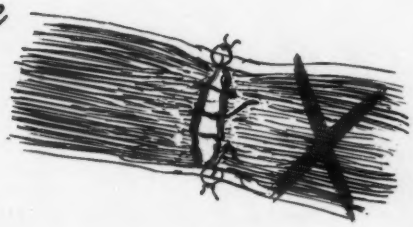
Fascia

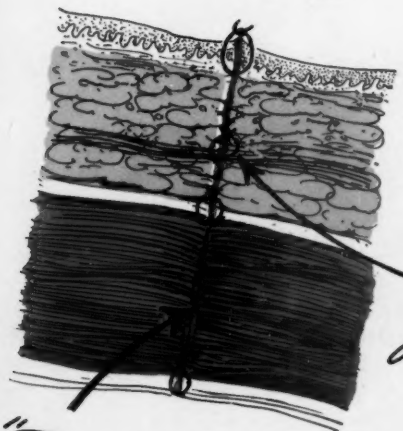
end-to-end or overlapped

Muscle and Fat

Fascia above and below sutured

Sutures in friable tissue cause necrosis. Thus, no holding power.





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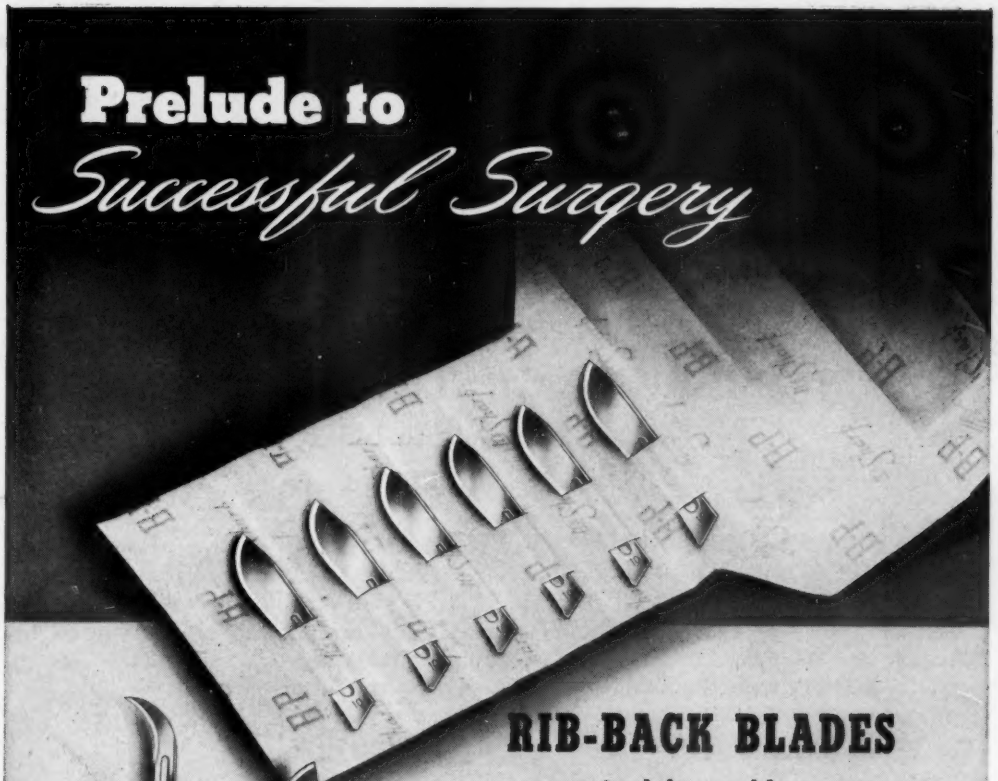

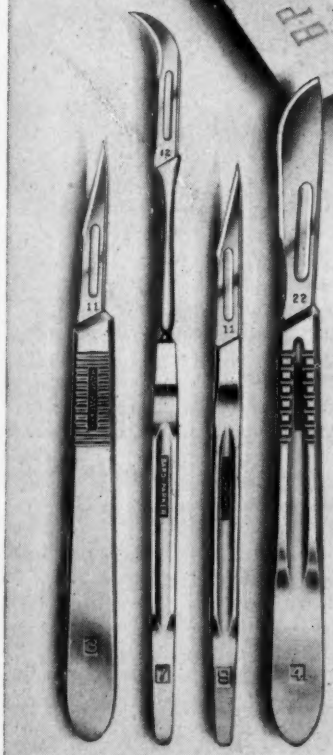

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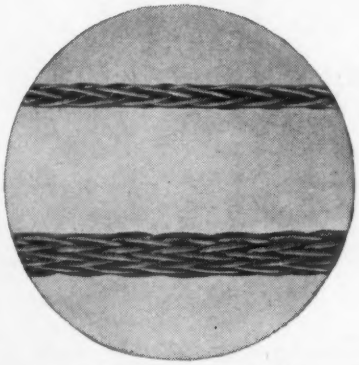

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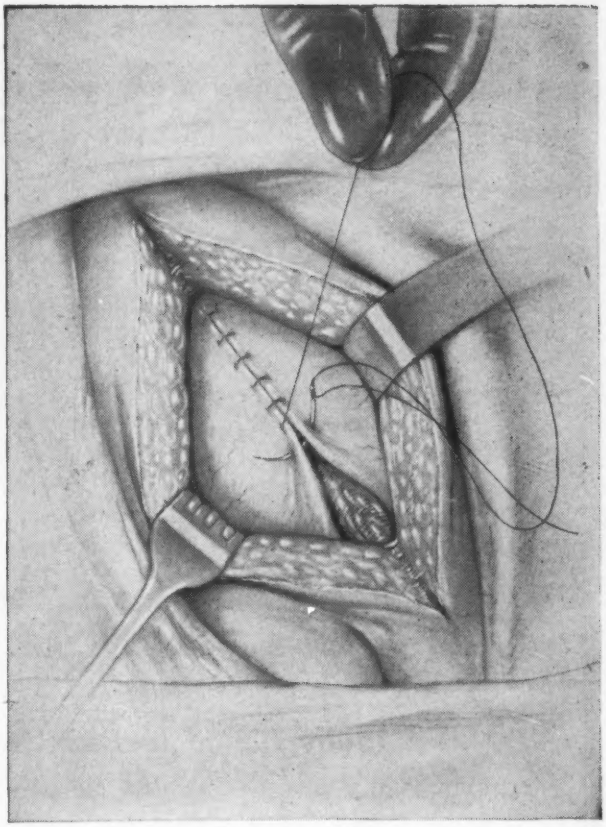

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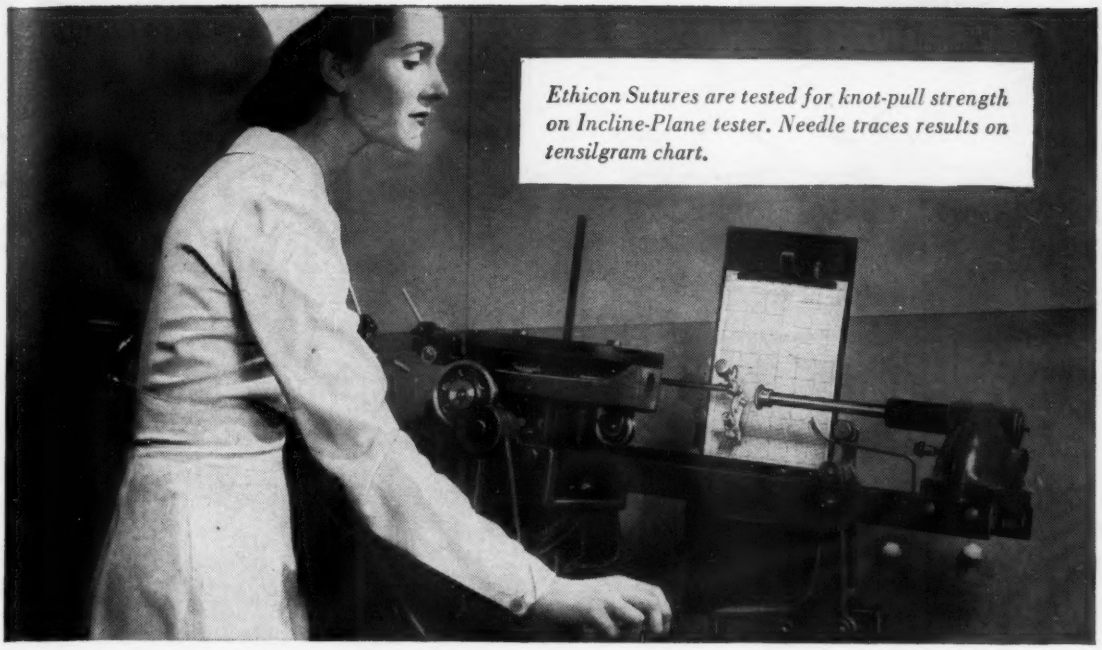

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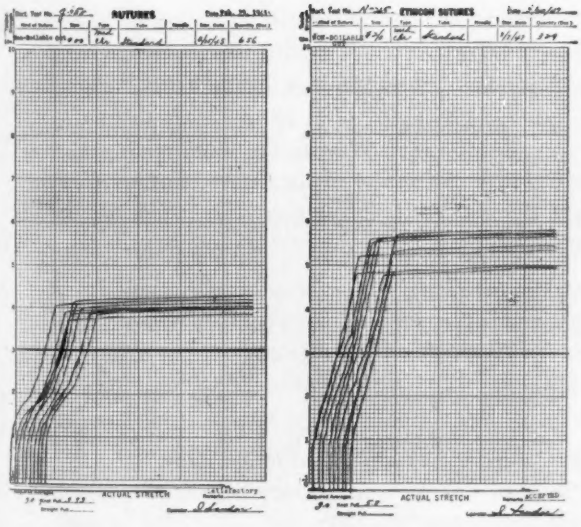

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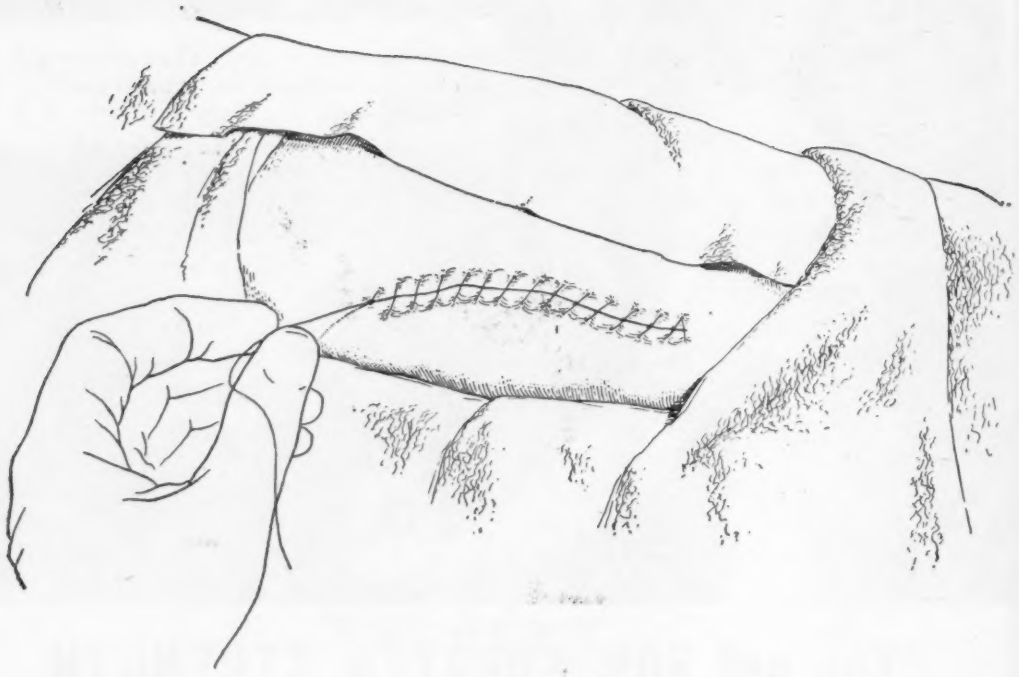

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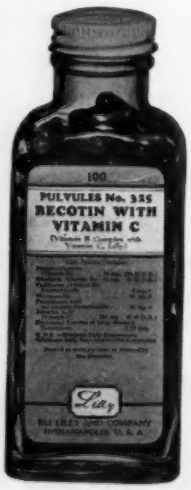

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SURGERY

VOL. 22 DECEMBER, 1947 NO. 6

Original Communications

STREPTOMYCIN IN SURGICAL INFECTIONS

IV. PERITONITIS

MAJOR EDWIN J. PULASKI,* MEDICAL CORPS, UNITED STATES ARMY, AND
COLONEL SAM F. SEELEY AND CAPTAIN CHARLES S. MATTHEWS,
MEDICAL CORPS, ARMY OF THE UNITED STATES

DURING the past ten years the mortality in peritonitis of various origins has been progressively lowered. Part of the reduction is undoubtedly to be attributed to the introduction and general use of increasingly more effective antibacterial agents. The sulfonamide drugs, penicillin, and streptomycin are, however, by no means solely responsible for the reduced mortality. The period in which these agents were coming into general use coincides with the period in which other adjuvant measures were also coming into general use and were being employed rationally as well as consistently. The routine management of peritonitis now includes, in addition to chemotherapy and antibiotic therapy, constant intestinal decompression, correction of perversions of the fluid and electrolyte balance, anticipation and correction of protein depletion, and measures to prevent as well as to treat thrombophlebitis and phlebothrombosis with threatening pulmonary infarction and embolism. All of these measures play an extremely important part in the reduced mortality of peritonitis, and they must be borne in mind in the evaluation of new forms of chemotherapy or antibiotic therapy.

ETIOLOGY OF PERITONITIS

Except in very young children peritonitis due to a single organism is relatively uncommon. The microorganisms responsible for this type of the disease are chiefly the beta hemolytic streptococcus group A, the pneumococcus, and the gonococcus. The sulfonamide drugs and penicillin are effective against these microorganisms and the mortality in this type of peritonitis has been correspondingly reduced as a result of their use. In peritonitis due to perforation of the hollow viscera, which is almost always associated with mechanical irritation, a polybacterial infection is the rule, comprising a variety of aerobic

Received for publication, July 29, 1947.

This project was carried out as a part of the study being made under the direction of the Army Medical Research and Development Board, Office of the Surgeon General.

*From The Surgical Research Unit, Brooke General Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

and anaerobic bacteria. Early studies[1] which indicated that peritoneal suppuration of fecal origin is due to the synergistic action of several bacterial species were later confirmed by Altemeier.[2] In an investigation of the bacterial flora of 100 cases of peritonitis of appendical origin, he was able to isolate an average of five different species of organisms from single peritoneal exudates. In some instances he isolated as many as sixteen different species. The microorganisms most commonly found, in association with other organisms which normally inhibit the gastrointestinal tract, were *Escherichia coli,* aerobic and anaerobic nonhemolytic streptococci, and Clostridia. Altemeier's experiments proved convincingly that *Esch. coli* was not the etiologic factor in peritonitis of appendical origin and also showed that it is not responsible for the odor of the exudate, as is commonly supposed. Previous studies[3] have showed that streptomycin has a potent antibacterial action on a wide variety of gram-negative and gram-positive organisms, particularly those of gastrointestinal origin. Studies of Pulaski and Sprinz,[4] which confirm the work of others,[5, 6] indicate that the drug diffuses readily into the peritoneal cavity in therapeutically effective concentrations following its parenteral administration. It might, therefore, be expected that this particular antibiotic would have a potent therapeutic effect in peritonitis of polybacterial etiology.

EARLIER STUDIES ON CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS

Experimental.—By ligating and then opening the appendix, Zintel and his associates[7] produced peritonitis in three series of dogs, each series consisting of fifteen animals. In the first series, which served as a control series, only one of the fifteen animals survived. In the second series, in which treatment consisted of large doses of streptomycin given intramuscularly, there were four survivals. In the third series, in which treatment consisted of a combination of penicillin intraumuscularly and sodium sulfadiazine intravenously, there were six survivals. These authors concluded that while streptomycin exerts a beneficial influence in experimental peritonitis in dogs, the therapeutic results are not as good as when a combination of penicillin and sulfadiazine is employed.

Silvani and his associates,[8] who carried out a similar experiment, concluded: (1) that streptomycin has no demonstrable suppressive effect on the bacterial flora of the peritoneal exudate, and that it is of little value either as a prophylactic or a therapeutic agent, in peritonitis in dogs; (2) that sodium sulfadiazine in large doses by the intravenous route also does not appreciably alter the bacterial flora of the peritoneum and has little or no protective effect against peritonitis in dogs; (3) that penicillin in large doses (equivalent to 1,500,000 units per day in man) effectively eradicates gram-positive bacteria. A significant number of the animals in the penicillin-treated group survived. In these dogs the residual bacterial component, which consisted chiefly of gram-negative bacteria, was relatively noninvasive and disappeared spontaneously.

Clinical.—The extensive literature on sulfonamide therapy may be summed up in the statement that most observers report some beneficial effects from its

ancillary employment in spreading peritonitis, but only equivocal results in cases in which there is considerable tissue necrosis or in which the microorganisms have localized due to abscess formation. Crile's report[9] that penicillin in massive doses by the intramuscular route is strikingly effective in peritonitis of appendical origin has been confirmed by Brown.[10]

To date only a few reports have been made on the use of streptomycin in the treatment of peritonitis. Hirshfeld and his associates[11] used it in twelve cases, in eight of which penicillin or the sulfonamides were used also. They attributed the absence of spectacular results to the inability of streptomycin to suppress certain gram-positive organisms, particularly the nonsporulating anaerobes. The report of the National Research Council on streptomycin[12] in the treatment of various infections included fifty-three cases of peritonitis due, in order of decreasing frequency, to appendicitis, postoperative infection, diverticulitis, intussusception, cancer, salpingitis, and abortion. Thirty-nine of the fifty-three patients recovered and twelve died. Of twenty-one patients who received streptomycin and "other forms of chemotherapy at the same time," eighteen recovered and three died. It was the opinion of the Council that these results were sufficiently encouraging to justify the advice that streptomycin be used in all cases of peritonitis in which the infecting microorganism was susceptible. The dosage advised was at least 2 Gm. per day for five days or longer.

ANALYSIS OF CASES

The sixty-three cases of peritonitis reported in this communication have been observed since November, 1945. They form a heterogeneous group in respect to etiology, management, scheme of dosage, and duration of thrapy. All of the patients were desperately ill, but they were predominantly young males in good health, either on active duty or recently separated from military service, and their nutritional status was usually excellent. The age range was from 7 to 62 years. Thirty-nine patients were between 17 and 30 years of age, and only six were over 45 years of age. One would expect good resistance to infection in such a group.

The majority of patients, in addition to streptomycin, had intensive supportive therapy, including constant intestinal decompression.

The results of therapy in twenty-one cases of peritonitis in which only streptomycin was used are presented in Table I. In Table II are presented the results of therapy in forty-two other cases in which streptomycin therapy was combined with penicillin therapy and, in some instances, with the administration of sulfadiazine also. Of the sixty-three patients, five died and eighteen others either showed no results at all from streptomycin therapy or showed improvement only when other therapeutic methods were employed, such as drainage of a periappendical abscess.

There are no control cases in this series. Results are stated entirely from the standpoint of whether or not they could be attributed to the use of streptomycin. A patient was regarded as benefited by it if he had the type of rapid, uncomplicated convalescence which could scarcely have been hoped for in the light of the disease process.

APPENDICAL PERITONITIS

Of thirty-nine patients with peritonitis of appendical origin, seventeen had spreading peritonitis and twenty-two localized peritonitis (Tables I and II). One patient with spreading peritonitis and one with localized peritonitis died; both were treated only with streptomycin. The patient with spreading peritonitis was a 49-year-old man with severe diabetes mellitus and arteriosclerotic heart disease. Streptomycin was not regarded as effective because his improvement was slow clinically and subjectively. He died suddenly on the seventh postoperative day as the result of pulmonary infarction. He had received 0.25 Gm. of streptomycin intramuscularly every four hours, which is a relatively small dose.

The other death in this group occurred in a 58-year-old white man with localizing peritonitis and an appendical abscess. He had a vascular accident on the first postoperative day, manifested by coma, stiff neck and jacksonian convulsions. He died on the seventh postoperative day; autopsy revealed a recent subarachnoid hemorrhage and bilateral pulmonary tuberculosis. There was a thick abscess wall about the drainage tube. The general peritoneal cavity was free from infection. He had received 0.25 Gm. of streptomycin intramuscularly every three hours from the time of operation until death. It should

TABLE I. RESULTS OF STREPTOMYCIN THERAPY IN TWENTY-ONE CASES OF PERITONITIS

NUMBER OF CASES	SOURCE OF INFECTION	TYPE	DAYS TREATED	DAILY DOSAGE (IN GM.)	RESULT
3	Appendicitis	Spreading	8	3.0	Good; rapid uneventful convalescence in each instance
1	Appendicitis*	Spreading-localizing	14	3.0	Good; mass completely disappeared in ten days
1	Appendicitis	Spreading	7	1.5	Doubtful; slow unspectacular improvement, death from pulmonary infarct
4	Appendicitis	Localizing	10	2.4	Good in 2 cases Equivocal in 1 case with palpable mass Doubtful in 1 case, death from subarachnoid hemorrhage
5	Appendicitis	Localizing	13	1.0	Doubtful in all; improvement coincident with drainage of abscess
2	Perforated carcinoma of sigmoid; drainage; abdominoperineal resection	Spreading	13	2.4	Good; rapid localization and elimination of the infection
3	Volvulus; post-anastomotic fistula of colon; perforated duodenal ulcer; operation	Localizing	9	1.0	Doubtful in all; peritonitis minimal in volvulus; improvement in others coincident with surgical drainage
1	Pelvic inflammatory disease	Localizing	14	1.0	Doubtful; slow steady improvement
1	Gunshot wounds, multiple	Spreading	1	1.0	Poor; death from sepsis

*No operation.

TABLE II. RESULTS OF STREPTOMYCIN-PENICILLIN THERAPY (WITH AND WITHOUT SULFADIAZINE) IN FORTY-TWO CASES OF PERITONITIS

NUMBER OF CASES	SOURCE OF INFECTION	TYPE	STREPTOMYCIN*		PENICILLIN* (UNITS x 1000)			SULFADIAZINE† (NUMBER OF CASES)	RESULT
			DOSAGE (IN GM.)	DAYS TREATED (AVERAGE)	120 TO 249	250 TO 499	500 TO 800		
6	Appendical	Spreading	4.0	7	4	2		1	Good in all; 1 pelvic abscess, with absorption, 1 trivial wound infection
4	Appendical	Spreading	3.0	12		1	1	1	Good in all; dramatic result in 1 nonsurgical case; 2 patients had myocardial disease
2	Appendical	Spreading	3.0	12		1	1		Good; previous therapy ineffective
4	Appendical	Localizing	2.4	7	1	2	1		Good in 2 nonsurgical cases;‡ doubtful in 2 cases, recovery unspectacular
1	Appendical	Localizing	2.0	10			1		Good‡
8	Appendical	Localizing	1.5	14	4	3	1	2	Good in 5 cases Poor in 3 cases, though no complications occurred; dosages small
4	Perforated viscera: duodenum		3.0-1.6	26		4			Good; 1 patient treated without operation
3	Ileum		2.4		3			1	Good in 2 cases Doubtful in 1 case, due to pulmonary complications
3	Colon		4.0-3.0	9	1	2		1	Excellent; 2 perforations of sigmoid, 1 postoperative peritonitis
5	Multiple gunshot & stab wounds		4.0-0.6	11	5			4	Poor; 2 deaths from nonbacterial causes; 2 wound disruptions; 1 pelvic abscess; 1 unspectacular recovery: All dosages small
2	Parametritis		2.4-1.6	11	1			1	Dramatic

*Daily dosage.
†Daily dosage, 6 Gm.
‡After addition of streptomycin to other therapy.

be noted that the vascular accident which was responsible for his death occurred within twenty-four hours of operation.

In the patients who responded to therapy, the clinical course was strikingly similar. In each instance the infection was controlled very rapidly. Distention and rigidity gradually subsided, ileus disappeared, and in all instances by the fourth day after operation there was passage of gas per rectum. Progressive localization of the process to the right lower quadrant of the abdomen or to the pelvis was notable. By the fourth or fifth day after operation the patient was free of discomfort and was on a selected diet. By the tenth day the temperature and pulse were normal.

The three patients treated without operation recovered as rapidly and as uneventfully as the patients who were submitted to surgery. Two of the three

had localized peritonitis. In the third case the process was spreading when the patient was first seen but was rapidly localized to the right lower quadrant (Fig. 1). Treatment consisted of 0.5 Gm. of streptomycin intramuscularly every four hours over a period of fourteen days. When interval appendectomy was performed six weeks after the original illness, there was no evidence of peritonitis.

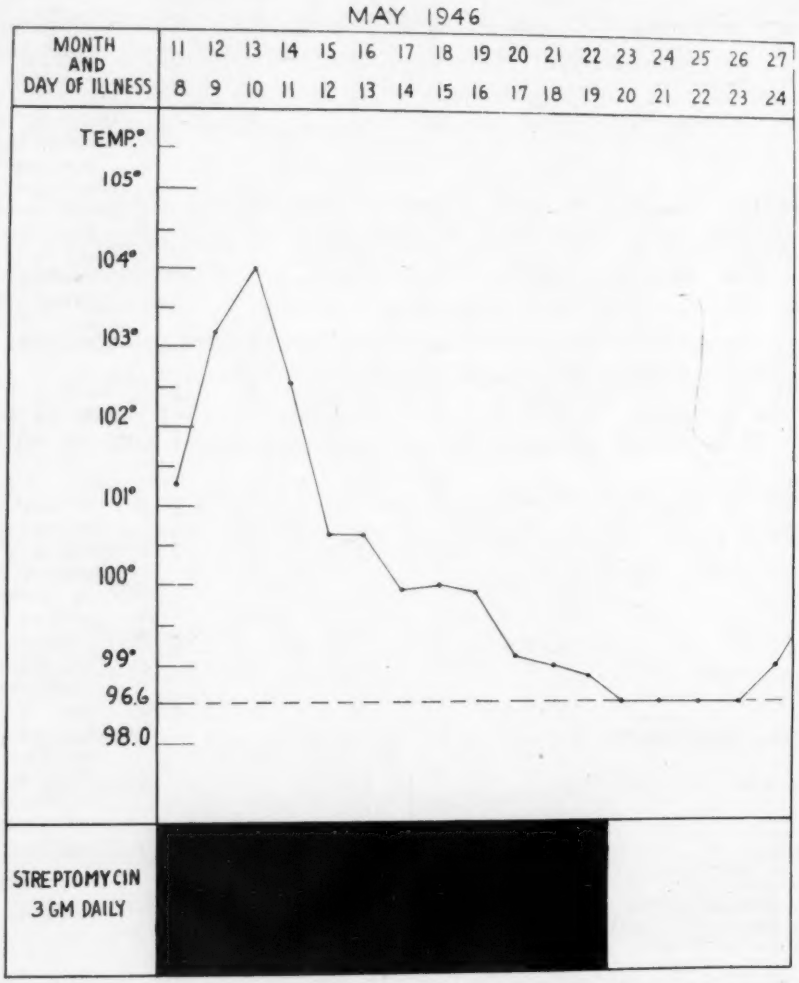

Fig. 1.—Localizing peritonitis of appendical origin. No operation was done. Regression of large mass in right lower quadrant could be followed from day to day.

Certain other cases are deserving of special mention. One patient, who apparently had a localizing type of peritonitis, was submitted to appendectomy and drainage of an abscess on the fifth day of illness. He had a very stormy postoperative course, characterized by recurring chills and temperature elevations to 106° F. The liver became enlarged and tender and he was slightly jaundiced. All the evidence pointed to a diagnosis of pylephlebitis. Recovery with uncomplicated wound healing followed the administration of 2.5 Gm. of streptomycin in divided doses daily for fourteen days, supplemented by the usual supportive therapy. The drug was considered lifesaving in this case. In

two other cases, however, in which streptomycin was used in conjunction with appendectomy and drainage of well-localized appendical abscesses, it was thought that the uneventful recoveries were quite as likely to have ensued without adjuvant antibiotic therapy as with it.

Four patients developed residual abscesses, while one patient developed a pelvic abscess twenty-eight days after drainage of an appendical abscess. In the interim, combined penicillin and sulfadiazine therapy had been given, with not particularly striking results. Parenteral streptomycin therapy was followed by prompt resolution of the abscess and prompt recovery without further surgery (Fig. 2). Two patients with subhepatic abscesses and one with a

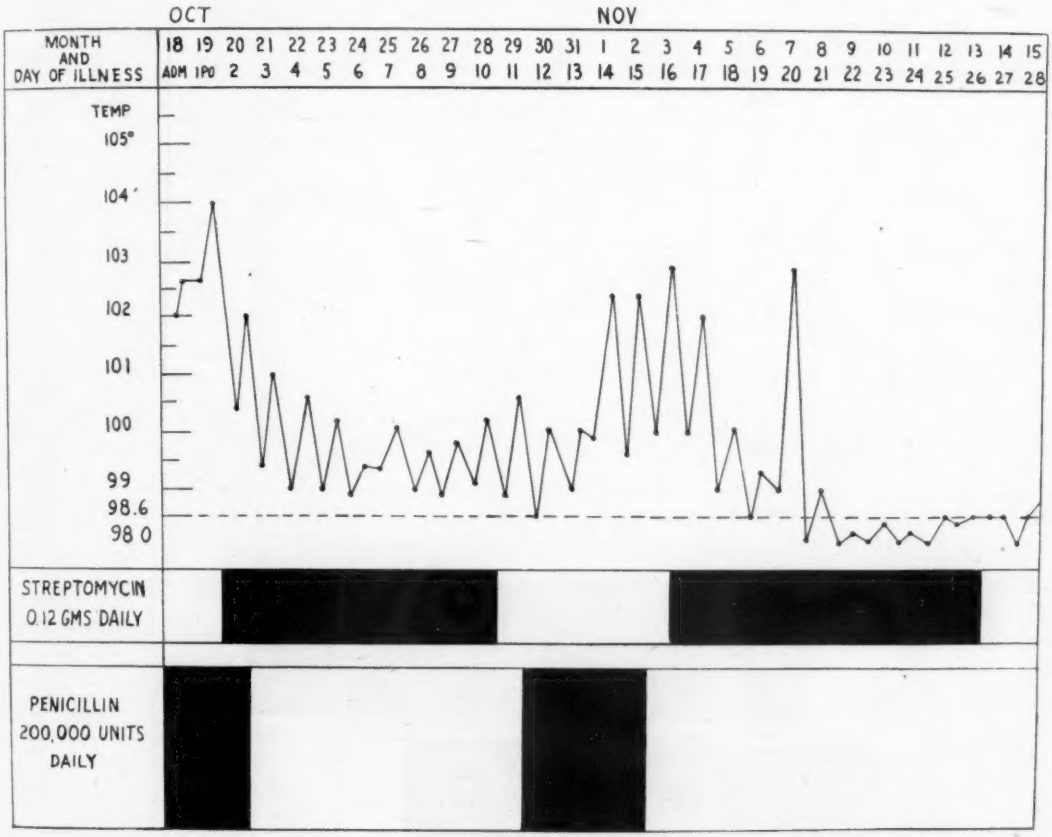

Fig. 2.—Spreading peritonitis of appendical origin. On the ninth postoperative day the patient developed a pelvic mass on right side. Two days later streptomycin was discontinued. The mass increased in size in spite of penicillin therapy, and streptomycin was resumed. There was spontaneous absorption and resolution. Rise of temperature to 103° F. on the twentieth postoperative day was due to a streptomycin reaction.

suprahepatic abscess following rupture of the appendix with spreading peritonitis were treated by streptomycin therapy in conjunction with drainage. Two recovered uneventfully. The third later required surgical excision of a persistent fistulous tract.

Twelve patients with spreading peritonitis of appendical origin were treated by both streptomycin and penicillin supplemented, in two cases, by sulfadiazine (Table II). Results were good to striking in every case (Fig. 3). Two

patients recovered in the face of myocardial disease, and a really dramatic response was obtained in another patient who was not operated upon.

Two of thirteen patients with localizing peritonitis (Table II) showed rapid improvement after the institution of therapy and did not require emergency operation (Fig. 4). In six other cases the results were good although not remarkable. In two of the remaining cases the response was doubtful and

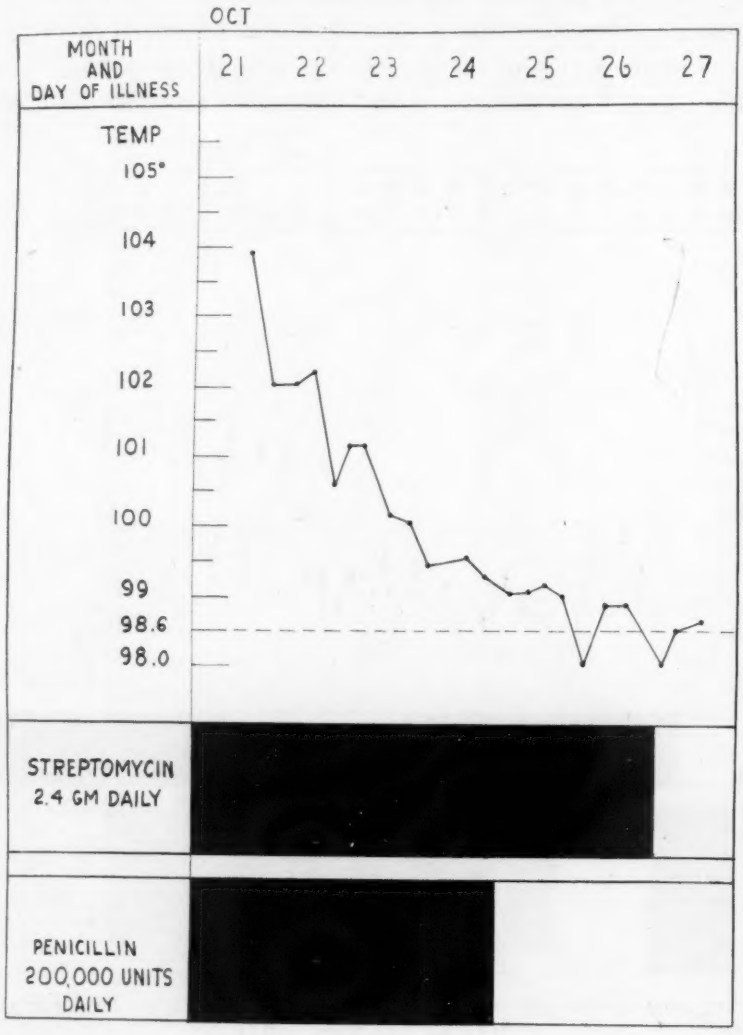

Fig. 3.—Localizing peritonitis of appendical origin. Recovery was rapid and uncomplicated after surgery.

in three cases there were no results at all. One patient in this group developed a pelvic abscess which required drainage on three occasions. In another case the stump of the appendix blew out, but the resulting fecal fistula fortunately exteriorized and ultimately closed spontaneously. In still another case extension of the infection to the subphrenic space was suspected, but abscess formation did not follow.

PERITONITIS OF NONAPPENDICAL ORIGIN

Seven patients with peritonitis of nonappendical origin were treated only with streptomycin (Table I). There was one death, from sepsis, in a patient with multiple gunshot wounds. He was moribund when first seen, on the seventh day of illness, and died within twenty-four hours. In two cases the results were excellent. One of these patients had been submitted to abdomin

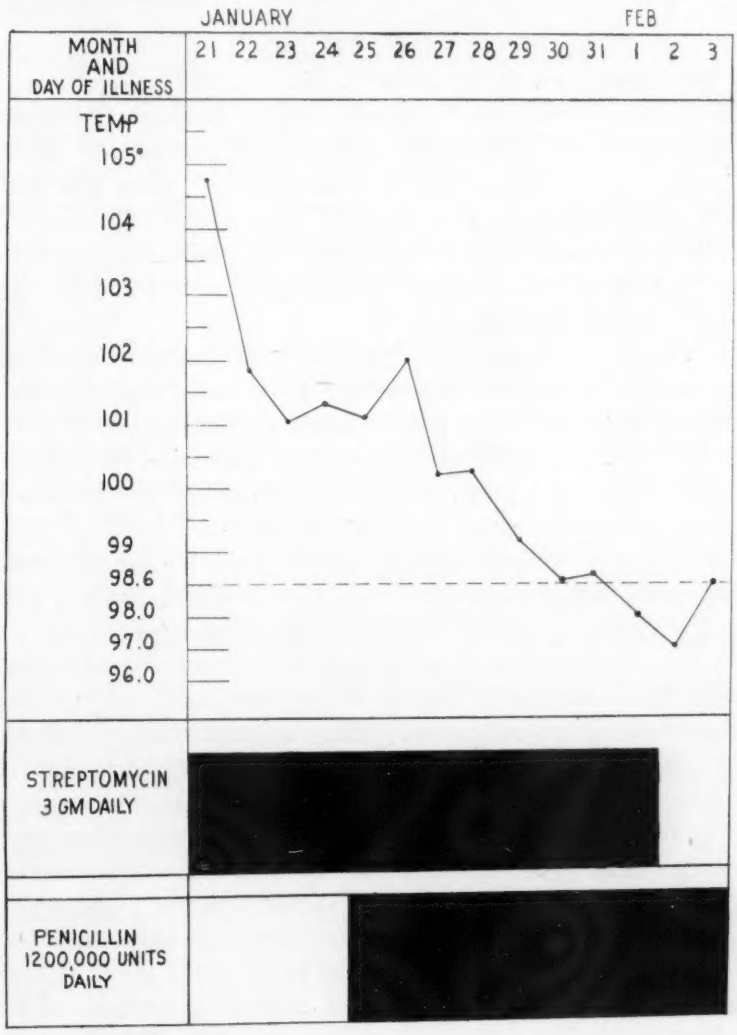

Fig. 4.—Localizing peritonitis of appendical origin. No operation was done. The ileus was uncontrolled after three days of streptomycin therapy. The course was uncomplicated after penicillin was added to the regimen.

perineal resection. The other had carcinoma of the sigmoid, which had ruptured into a loop of the ileum and then into the free peritoneal cavity. Drainage of the subsequent abscess yielded a thin pus, without odor, which grew only nonhemolytic streptococci. These organisms were moderately susceptible to streptomycin. Results in the two other cases in this group were doubtful in that improvement either was slow or followed the use of surgical drainage.

There were two deaths in seventeen patients with nonappendical peritonitis treated by streptomycin and penicillin with or without sulfadiazine (Table II). Both occurred in patients with stab wounds of the abdomen and both were due to vascular collapse and not to bacterial infection. In all cases of early spreading peritonitis the response was dramatic. The two patients who showed no improvement both had small doses of streptomycin; in one of these cases recovery was complicated by pulmonary atelectasis and pneumonia.

COMMENT

Of the five deaths which occurred in the sixty-three cases of peritonitis presented in this communication, three were due to nonbacterial causes. In the other two cases, both of which were instances of generalized fibrinopurulent peritonitis, streptomycin was added to other therapy when the patients were already moribund, apparently as a "panic" measure. Eighteen of the fifty-eight patients who recovered were treated only with streptomycin; the remaining forty patients were treated with streptomycin and penicillin, supplemented in ten cases by sulfadiazine.

Immediate dramatic results were seldom observed following the administration of streptomycin, whether it was used alone or in combination with penicillin, although in both spreading and localized peritonitis recovery was thought to be smoother and more rapid when the drugs were used in combination. In no instance could any cumulative effect be attributed to the administration of streptomycin and sulfadiazine in combination.

Streptomycin was undoubtedly more effective in early spreading peritonitis, although immediate dramatic results were not the rule, whether it was used alone or with penicillin. Resolution of established peritoneal suppuration in the streptomycin series was of approximately the same pattern as is seen in patients receiving penicillin in excess of 800,000 units. While results were generally less striking when streptomycin was employed in infections which had already localized, the impression was received that resolution occurred more rapidly in such cases when penicillin was also used. The combination gave particularly good results in three instances of pelvic inflammatory disease in which no demonstrable result had been achieved by penicillin therapy alone.

The dosage of streptomycin employed varied between 1 and 4 Gm. per day, administered by the intramuscular route in divided doses at three- or four-hour intervals. In a few instances streptomycin in amounts up to 0.5 Gm. was introduced into the peritoneal cavity at the time of operation. There was no apparent adverse effect. The dosage of penicillin ranged between 120,000 and 600,000 units per day. The average dose of sulfadiazine was 6 Gm. daily.

Consistently beneficial effects could never be attributed to streptomycin when the dosage was 2 Gm. per day or less, whether it was given alone, with sulfadiazine, or with penicillin in amounts of 240,000 units per day or less. No harmful effects were noted in consequence of daily dosages of 3 Gm. per day for ten to fourteen days, although minor untoward reactions occurred in approximately 20 per cent of the cases. Patients who received 3 Gm. per day of streptomycin alone, or 2.5 Gm. in combination with an average of 480,000 units of penicillin, had the most satisfactory postoperative convalescence. The re-

sponse to streptomycin therapy was practically always indifferent when inadequate doses were used (1.5 Gm. per day or less).

On the basis of this small series of cases it is impossible either to ascribe consistently beneficial effects to streptomycin therapy in peritonitis or to deny the possibility of therapeutic benefits in early established peritoneal suppuration. Clear-cut beneficial results were generally more apparent in spreading than in localized processes.

SUMMARY AND CONCLUSIONS

1. Sixty-three patients with peritonitis of various etiologies, of whom five died, received adjuvant streptomycin therapy alone or in combination with penicillin; sulfadiazine was added in a few cases.

2. The beneficial effects of streptomycin therapy in early spreading peritonitis closely paralleled those observed in cases in which large doses of penicillin were given. Streptomycin did not seem to be of particular value in localized peritoneal suppuration.

3. On the basis of these preliminary studies, it is apparent that streptomycin is not a panacea, yet has a valuable place in the treatment of peritonitis. Used alone it is especially effective in spreading and in localizing types of infection without a palpable mass. Used in conjunction with penicillin it is effective in many patients who fail to respond to penicillin alone or to penicillin combined with sulfonamides.

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STUDIES IN EXPERIMENTAL FROSTBITE

I. The Effect of Heparin in Preventing Gangrene

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THE confusion which exists in the treatment of frostbite during the early phase is due largely to a difference of opinion regarding the chief mechanism by which permanent ischemic damage is produced. Some investigators have felt that the major difficulties are the result of reduced blood flow consequent to the swelling of the limb from edema and extravasation. They have directed treatment toward reducing the swelling and diminishing tissue metabolism by prolonging the period of thawing and by local cooling of the injured part. Others have felt, on the other hand, that the principal harm results from prolonged intense vasoconstriction and eventual thrombosis of arteries and arterioles. They have concentrated therapeutic efforts on elimination of vasospasm and prompt restoration of the best possible circulation. There is much to support this second concept.[1] An important additional means of treatment has been introduced recently by experiments suggesting that anticoagulants may be effective in preventing thrombosis and gangrene.

In 1944 Brambel and Loker[2] used dicumarol, sympathetic blocks, and boric acid compresses to treat a patient in whom incipient bilateral gangrene of the toes had developed following frostbite. Some difficulty with bleeding from ulcerated areas occurred, but healing took place with the loss of only the distal phalanx of one toe. Although it was conjecturable whether major amputation would otherwise have been required, they had the impression that anticoagulant therapy might have been responsible for the good result, and suggested study of its usefulness in other cases of frostbite.

In 1945 Lange and Boyd[3] reported experiments in frostbitten rabbits which were convincing of dramatic efficacy of heparinization in the prevention of gangrene. Subsequently Lange and Loewe[4] reported that heparin was also brilliantly effective in preventing gangrene of skin in experimental contact frostbite in human volunteers. Since the present investigation was completed, another report by Friedman, Lange, and Weiner[5] has appeared confirming the usefulness of heparin in preventing gangrene following experimental frostbite in rabbits. Their investigation demonstrated that the chief pathologic changes following the initial vasoconstriction are vascular engorgement with conglutination of erythrocytes followed subsequently by true agglutinative thrombi, and that heparinization tends to prevent the formation of these thrombi.

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These studies are of such importance in the pathology and treatment of frostbite that we believed it was worth while to carry out similar investigations. It was our desire to see whether the good results obtained by Lange and his co-workers could be duplicated in another laboratory and with such uniformity as to justify the hopes which their reports naturally have raised. It was further hoped that more precise data could be accumulated concerning the relationship to the ultimate result of such factors as the degree of cold, the duration of exposure, and the extent of the area frozen, as well as the time of beginning treatment, the duration of treatment, and its intensity. Unfortunately, the initial phases of this problem have proved so difficult that the project has not been completed. Since these studies have confirmed the fact that adequate heparinization is sometimes effective in preventing gangrene in experimental frostbite but have at the same time demonstrated that this treatment is by no means uniformly successful, it is felt advisable to present our preliminary investigations. This is not done in order to discourage the use of anticoagulants in frostbite, but rather to dispel any false sense of security which may prevail based upon the notion that such treatment may be regularly effective even in the severest cases.

MATERIALS AND METHODS

Domestic rabbits of mixed breed weighing from 2 to 3 kg. were used. The hind limb to be frozen was carefully depilated at least twenty-four hours before freezing in order to make sure that no significant injury to the skin had occurred. The rabbits were anesthetized for freezing with nembutal given intravenously. In a few experiments the limb was immersed directly in an ether-dry ice mixture; in the majority the limb was covered first with a rubber condom boot, care being taken to prevent tearing of the boot or spilling over of the ether into it. In all instances constriction of the limb was studiously avoided. The degree of coldness of the solution varied, as well as the duration of the exposure. In each freezing experiment it was noted whether or not actual freezing of the part had occurred, and in the rare instances in which solid freezing did not take place the animal was discarded from the series. In all cases the limb was immersed up to the level of the hock. In most of the experiments the frozen limb was gently sponged with 1:1,000 aqueous zephiran and covered with sulfathiazole ointment and sterile dressing applied snugly but in such a way as to cause no constriction. The dressings were changed occasionally but were continued until recovery was complete or gangrene was obviously well established. The details of each freezing experiment are recorded in the results.

Varying amounts of heparin in aqueous solution were administered intermittently by the intravenous route. Clotting time was determined upon some animals by the capillary tube method with blood obtained by puncture of the ear; in others by the method of Lee and White[6] with blood removed by cardiac aspiration.

RESULTS

This report is based upon observations of 66 rabbits, one hind limb of which was solidly frozen. Excluded are 2 rabbits in which the exposed limb did not become solidly frozen, 5 rabbits which died of unknown causes, and 16 which died during the course of anticoagulant therapy before the outcome of the experiment could be determined. Of the 16 rabbits which died under heparin treatment the majority showed large retroperitoneal hemorrhage or other evidence of bleeding.

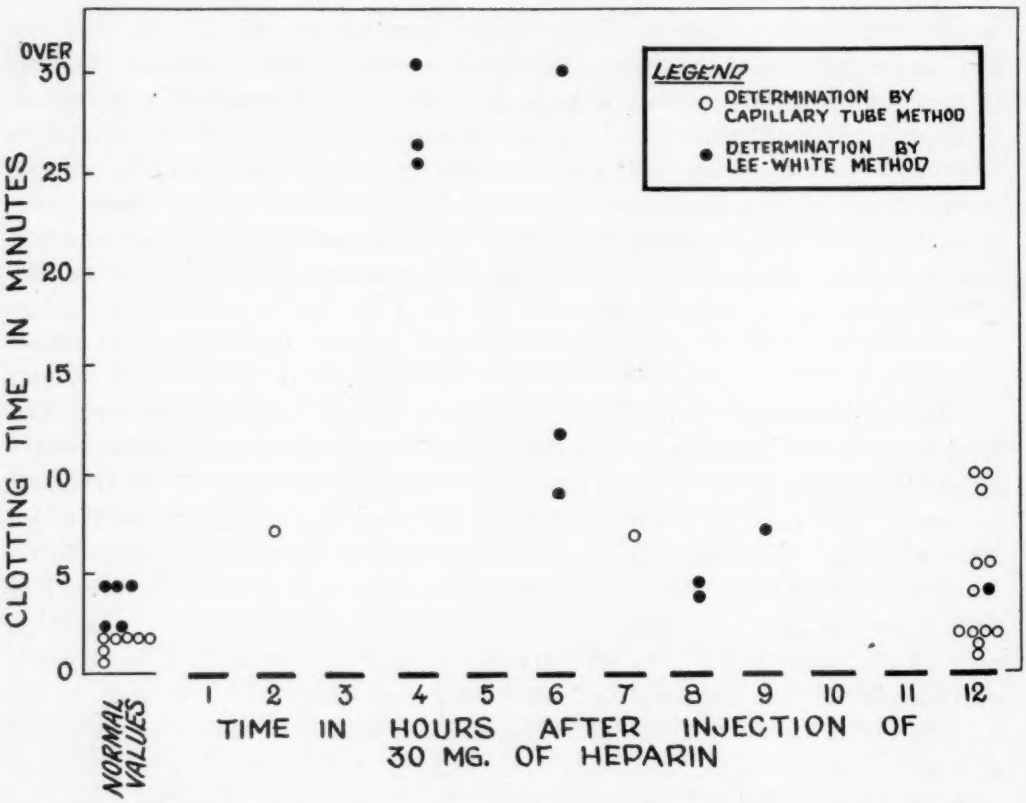

Fig. 1.—Clotting time values after single intravenous injection of 30 mg. heparin.

It was not found practicable to perform determinations of clotting time at frequent intervals during the course of treatment in order to be certain that in any given animal the prolongation of clotting time was constantly maintained during anticoagulant therapy. Not only is it impossible to remove blood by cardiac puncture at frequent intervals for a period of five or six days without causing death in a large number of animals, but the removal of sufficient blood for the more reliable Lee-White method during such a period would produce a severe anemia. Indeed, it was found to be impracticable to secure blood for the capillary tube method five or six times daily by puncture of the ear since such efforts rapidly obliterated by local injury or extravasation the veins necessary for intravenous therapy. An effort to evaluate the

efficacy of varying doses of heparin had to be made by controlled experiments upon a number of animals rather than by routine determinations upon each one.

Since Lange and Boyd had given heparin every twelve hours intravenously in 30 mg. doses, the effect of this treatment was first investigated. The results are recorded in Fig. 1. With the capillary tube method, the values of normal control clotting time varied from 1 to 2 minutes, averaging 1.8 minutes. Twelve hours after injection of 30 mg. of heparin the clotting time had returned to normal in one-half of the animals; in the other one-half it

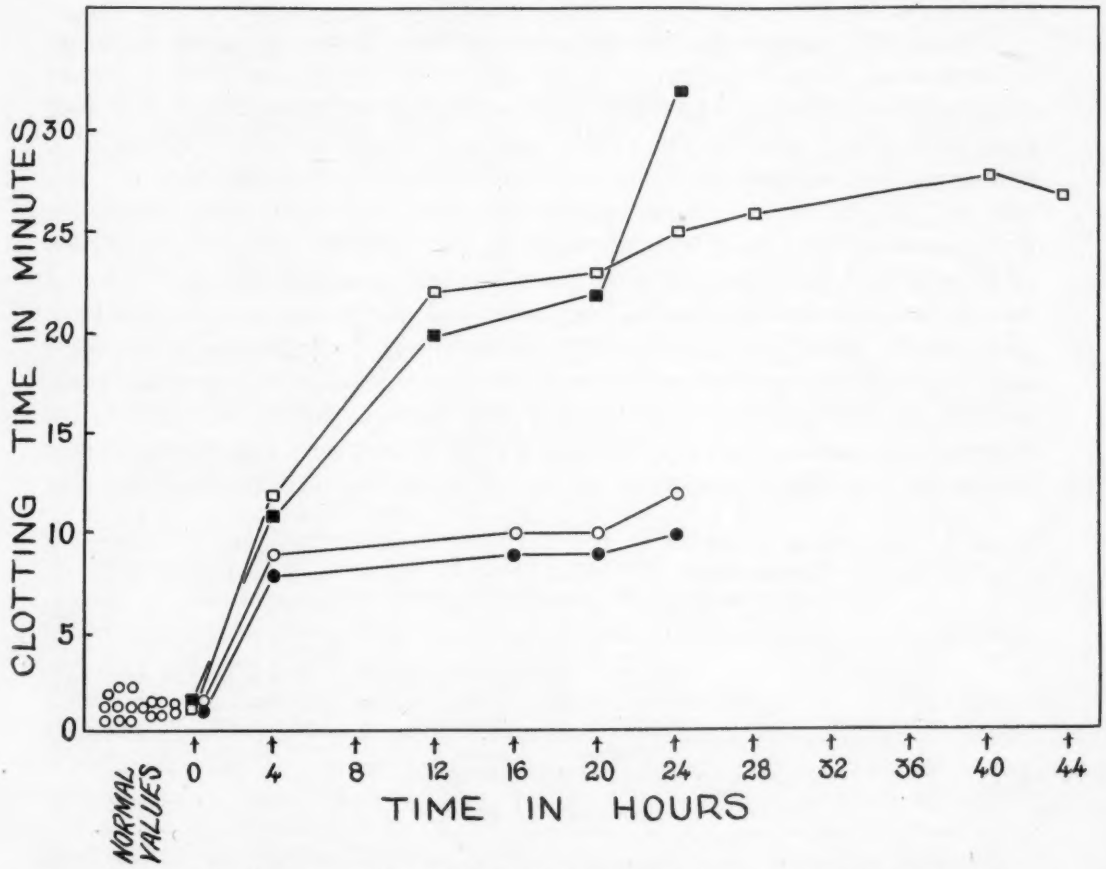

Fig. 2.—Clotting time values during course of heparin treatment. The values designated by the open and by the shaded squares represent studies in two animals which were given 20 mg. of heparin intravenously at intervals of four hours; those represented by the open and shaded circles, studies in two animals treated with 10 mg. of heparin intravenously at intervals of four hours. Blood for clotting time determination was drawn in each instance immediately before heparin was administered.

ranged from 4 to 10 minutes. The control coagulation time values with the Lee-White method ranged from 2.5 to 4.5 minutes, averaging 3.7. The clotting time was well prolonged four hours after injection of heparin but became less prolonged thereafter, and in 3 of 4 animals was within the normal range from eight to twelve hours after injection. The conclusion was reached that one could not rely upon 30 mg. of heparin given every twelve hours to provide constant prolongation of coagulation time.

In Fig. 2 data are recorded showing that 10 mg. of heparin given intravenously every four hours keeps the clotting time not less than from 8 to 12 minutes, and that 20 mg. of heparin given in similar fashion maintains the clotting time between 20 and 30 minutes. A few additional studies confirmed the observations from the 4 experiments which form the basis for this chart. It will be noted that the normal control values with the Lee-White method were different in the two sets of experiments recorded in Figs. 1 and 2; these sets of experiments were carried out by different investigators. Although the results of this determination vary somewhat with different observers, they are reasonably reliable in the hands of one observer.

The initial experiments are recorded in Table I and represent an effort to determine whether gangrene following severe degrees of direct contact freezing can be prevented by small or large amounts of heparin. The depilated hind limb of the anesthetized rabbit was immersed without protection of a rubber boot up to the hock in an ether-carbon dioxide snow mixture at from –20° to –40° C. No dressings were placed upon the frozen limb. Extensive gangrene developed in all animals whether the limb was frozen 5, 20, 30, 50, or 90 minutes. Four animals were given a single 30 mg. injection of heparin 30 minutes after freezing for one-half hour, and one was treated at four-hour intervals for sixty-four hours with the same dose. Two animals which were subjected to freezing of a foot for one hour were treated at four-hour intervals with 20 mg. of heparin for a forty-eight hour period, 2 others for a ninety-six hour period, and 2 others for 144 hours. One rabbit, one foot of which was frozen for 90 minutes, received 30 mg. of heparin every twelve hours for

TABLE I. RESULTS OF EXPOSURE OF THE DEPILATED UNPROTECTED FOOT OF RABBITS TO ETHER-CARBON DIOXIDE SNOW MIXTURE AT FROM –20° TO –40°C., WITH AND WITHOUT HEPARIN THERAPY; NO DRESSING APPLIED TO FROZEN LIMB

TREATMENT	NO. OF ANIMALS	RESULT	
		GANGRENE OF ENTIRE AREA FROZEN (NO. OF ANIMALS)	GANGRENE NEARLY TO UPPER LIMIT OF AREA FROZEN (NO. OF ANIMALS)
Exposure: 5 minutes			
None	1	1	
Exposure: 20 minutes			
None	2	2	
Exposure: 30 minutes			
None	1	1	
30 mg. heparin 30 min. after freezing	4	4	
Same continued q. 4 hr. for 64 hr.	1	1	
Exposure: 60 minutes			
20 mg. heparin 30 min. after freezing and q. 4 hr. for 48 hr.	2	2	
Same for 96 hr.	2	2	
Same for 144 hr.	2		2
Exposure: 90 minutes			
None	1	1	
30 mg. heparin q. 12 hr. for 48 hr.	1	1	

forty-eight hours. The extent and character of the gangrene were precisely the same in the treated and untreated animals with the exception of the 2 rabbits treated with heparin at four-hour intervals for six days; in these two complete dry gangrene extended almost but not quite up to the upper level of the frozen area.

The second set of experiments are recorded in Table II. The depilated hind limb of the anesthetized rabbit was covered with a rubber condom boot and was immersed up to the hock for varying periods in ether maintained at a temperature of from –12° to –20° C. By placing a beaker filled with ether inside a larger container filled with ether and dry ice and by stirring the fluid in the beaker and constantly checking its temperature with a thermom-

TABLE II. RESULTS OF EXPOSURE OF DEPILATED FOOT OF RABBIT, PROTECTED BY CONDOM BOOT, IN ETHER KEPT AT FROM –12° TO –20° C., WITH AND WITHOUT HEPARIN THERAPY

TREATMENT				RESULT				
AMT. HEPARIN AND FREQUENCY OF INJECTION	TIME AFTER FREEZING RX BEGUN	DURATION OF RX (IN HR.)	NO. OF ANIMALS	NO GANGRENE OR ULCER (NO. OF ANIMALS)	SUPERFICIAL ULCER ONLY (NO. OF ANIMALS)	GANGRENE LIMITED TO TOES (NO. OF ANIMALS)	GANGRENE COMPLETE UP TO WITHIN 1 TO 2 CM. OF UPPER LEVEL OF FREEZING (NO. OF ANIMALS)	GANGRENE OF ENTIRE FOOT (NO. OF ANIMALS)
Exosure: 60 minutes								
None			3					3
10 mg. q. 4 hr.	30 min.	24	1					1
10 mg. q. 4 hr.	30 min.	48	1					1
10 mg. q. 4 hr.	30 min.	96	1					1
10 mg. q. 4 hr.	30 min.	120	1					1
20 mg. q. 4 hr.	30 min.	48	1					1
20 mg. q. 4 hr.	30 min.	96	2				1	1
20 mg. q. 4 hr.	30 min.	144	2					2
30 mg. q. 4 hr.	30 min.	48	1			1		
30 mg. q. 4 hr.	30 min.	96	1		1			
30 mg. q. 4 hr.	30 min.	120	1		1			
Exposure: 45 minutes								
30 mg. q. 12 hr.	30 min.	72	2					2
Exposure: 30 minutes								
None			7					7
20 mg. q. 4 hr.	30 min.	72	1					1
20 mg. q. 4 hr.	30 min.	96	1					1
20 mg. q. 4 hr.	30 min.	120	1				1	1
20 mg. q. 4 hr.	30 min.	144	3					3
20 mg. q. 4 hr.	2 hr.	144	2			2		
20 mg. q. 4 hr.	4 hr.	144	1				1	
20 mg. q. 4 hr.	10 hr.	144	1				1	
30 mg. q. 4 hr.	30 min.	64	1	1				
30 mg. q. 4 hr.	30 min.	120	1					1
Exposure: 15 minutes								
None			2				2	
Exposure: 10 minutes								
None			4				4	
20 mg. q. 4 hr.	30 min.	48	2		1	1		
20 mg. q. 4 hr.	30 min.	144	7	2	1		4	
20 mg. q. 4 hr.	10 hr.	144	1				1	
Exposure: 5 minutes								
None			1		1			

eter which was left in place, and by adding dry ice as needed to the outside mixture, it was not difficult to regulate the temperature. The frozen foot was kept entirely dry. Immediately after freezing, the limb was sponged with zephiran and covered with sulfathiazole ointment and sterile dressings.

Fifteen limbs were frozen for 60 minutes. The control animals had complete gangrene up to the upper level of freezing. Four were treated with 10 mg. of heparin every four hours for varying periods, 5 with 20 mg. and 3 with 30 mg. All save 4 had gangrene as extensive as that of the controls. In one rabbit treated for four days with 20 mg. doses, complete gangrene appeared but not quite up to the hock. One animal treated for forty-eight hours with 30 mg. doses had gangrene limited to the toes, whereas in 2 treated for 96 and 120 hours there were only small superficial ulcers and no deep gangrene.

In 13 animals the foot was frozen for 30 minutes. The 7 controls had complete gangrene of the entire frozen area. Two rabbits were given 30 mg. doses of heparin for 64 and 120-hour periods; in the first there was no gangrene but the second had gangrene of the entire foot. Five of the 10 rabbits treated with 20 mg. doses of heparin showed gangrene of the entire foot. In 3 the gangrene was of slightly less extent, and in 2 it was limited to the toes.

One foot each of 14 rabbits was placed in the freezing solution for only a 10 minute period. In the 4 control animals the gangrene was complete but involved an area extending only up to within 1 to 2 cm. of the upper level of freezing. One of the 2 rabbits treated for two days had gangrene only of some of the toes and the other had only a superficial ulcer. In 4 of the 7 rabbits treated for a six day period, however, there was as extensive gangrene as in the controls. In 2 no gangrene appeared; in the third there was only a superficial ulcer. Gangrene was complete in the one rabbit treated for six days in which treatment was begun ten hours after freezing.

In those rabbits in which gangrene was averted there was sensory loss in the foot during the period of observation, which, in general covered two weeks. In 3 rabbits the blood flow to one foot was completely occluded for 30 minutes and in 3 others for one hour by a rubber tourniquet tightly applied about the leg. None of these animals had gangrene or motor or sensory disturbance.

DISCUSSION

The first experiments recorded failed to demonstrate that small or larger amounts of heparin were effectual in preventing gangrene when the unprotected foot was frozen for rather long periods in a mixture kept at from –20° to –40° C. These experiments are of limited significance since there were few animals which were adequately heparinized for a prolonged period.

The second set of experiments deal with the treatment of frostbite of less extent than that treated by Lange and his co-workers. Lange and Boyd reported that of 11 anesthetized rabbits, the depilated hind limb of each of which was frozen up to the knee for from 45 to 90 minutes in a solution kept at from –12° to –20° C., 2 died of hemorrhage and 2 showed superficial necrosis of considerable extent, but these and the 7 other survivors recovered without loss of tissue.

Friedman, Lange, and Weiner have recently reported that there was no other evidence of gangrene than occasional small areas of focal necrosis in 13 rabbits in which the clotting time never fell below 30 minutes during treatment after freezing of a hind limb up to the knee for one-half hour in a mixture kept at –30° C., and in 4 of the 7 rabbits similarly prepared and treated in which the clotting time was not kept constantly so prolonged. These animals were sacrificed from two to nine days after freezing.

In the experiments which we have recorded the limb was similarly protected with a rubber boot, cleansed with a mild antiseptic solution, and dressed with sterile bandage after freezing. The area of limb exposed was less, being only up to the level of the hock rather than up to the knee. The time of exposure was reduced to as little as 10 minutes. Although Lange and Boyd give no detailed information in regard to heparin therapy, they imply that it was the same as they used in experiments in direct spot contact freezing in which they gave 30 mg. of heparin intravenously every twelve hours for a period of at least five days, beginning treatment from one-half to three hours after freezing ended. In the experiments of Friedman, Lange, and Weiner heparin was given in 50 mg. doses at twelve hour intervals. In some of our experiments the same daily dose of 60 mg. of heparin which Lange and Boyd used was given but in a manner which provides more constant prolongation of clotting time; namely, by administration at intervals of four hours. In other experiments 20 and 30 mg. of heparin were given every four hours. Control studies demonstrated constant prolongation of clotting time when 10 mg. of heparin was given at four hour intervals and greater prolongation when 20 mg. doses were used. Many of the animals in which 30 mg. of heparin were given at four-hour intervals and some of those similarly treated with 20 mg. doses died of hemorrhage before completion of the experiment.

It is difficult to explain why in our experiments, with exposure of a smaller area for a shorter interval of time and with a more efficient method of anticoagulant therapy, the results were so inferior to those reported by Lange and his associates. If we consider only those animals which were treated for five days or more, it is seen that deep gangrene was prevented in only 4 of 21 rabbits treated, an incidence of 19 per cent. If 3 animals are eliminated in which treatment was started after an interval of more than three hours after completion of freezing, 4 of 17 animals, or 23.5 per cent, escaped deep gangrene. Two additional animals had gangrene limited to the toes. If they are included, 6 of 17, or 35.3 per cent, escaped disabling permanent loss of tissue. This fact is in contrast to the protection against deep gangrene in all of the small group treated by Lange and Boyd, in all of the 13 rabbits treated by Friedman, Lange, and Weiner in which the clotting time did not fall below 30 minutes, and in 4 of 7 in which the clotting time was occasionally less.

There can be no doubt that in certain animals heparin therapy was responsible for preventing gangrene or lessening its extent. It will be noted that every untreated animal the foot of which was frozen during an exposure of 30 minutes or longer had complete gangrene up to the level of freezing, and that in untreated animals gangrene of only slightly less extent invariably

followed an exposure of 10 or 15 minutes. The 11 animals in which gangrene was averted or was limited to the toes or to superficial ulceration were all treated with heparin, as were the 4 rabbits exposed for 30 minutes or longer in which the gangrene, though extensive, did not include the proximal 1 or 2 cm. of the area frozen.

Unfortunately our experiments do not permit, we feel, clear-cut conclusions concerning certain important related problems. It is not clear from the data recorded in Table II, for example, that when four-hour heparin therapy begun within two hours of the termination of freezing was continued for five days or more, the results were better than when treatment was kept up for a shorter period. Six of the 17 rabbits (35.3 per cent) which were so treated for five days or more had no gangrene or only superficial ulceration or loss of toes, whereas 5 of 13 (38.5 per cent) treated for shorter periods recovered with similarly slight loss of tissue. On more careful analysis the results are seen to be rather contradictory. In the case of those animals in which the exposure was 10 minutes and in which treatment with 20 mg. of heparin was begun promptly and continued at four-hour intervals for forty-eight hours, only minor loss of tissue occurred, whereas this was true in only 3 of 7 rabbits treated similarly for six days. On the other hand, minor loss of tissue took place in 2 of 5 rabbits exposed for 30 minutes and treated promptly with heparin and for a period of five or six days, whereas both of the rabbits similarly exposed but treated with the same dose for shorter periods had complete gangrene of the foot.

It is of interest that 5 of 9 rabbits exposed for 10 minutes and treated promptly with heparin in 20 mg. doses given at four-hour intervals had no gangrene or had only slight loss of tissue (55.5 per cent), whereas such good results prevailed in only 2 of 8 rabbits (25 per cent) similarly treated after a 30 minute exposure, and in none of 5 treated in the same manner after a 60 minute exposure. In 1 of 2 rabbits, a foot of which was exposed for 30 minutes, treated promptly with heparin given in 30 mg. doses at four-hour intervals, no gangrene developed, and in all 3 similarly treated after a 60 minute exposure there were only superficial ulcers or gangrene limited to the toes. In contrast, all 4 rabbits treated with 10 mg. doses after a 60-minute exposure had complete gangrene of the foot. The 5 rabbits treated with heparin given at intervals of twelve hours, or at more frequent intervals but after a delay before onset of treatment of from four to ten hours following freezing, had extensive gangrene, although in 2 it was slightly less extensive than that observed in the controls. Five of 9 treated rabbits (55.5 per cent) had only minor loss of tissue or no gangrene at all in the group exposed for 10 minutes, 3 of 12 (25 per cent) exposed for 30 minutes, and 3 of 12 (25 per cent) exposed for 60 minutes. The last group includes some animals treated only with 10 mg. doses of heparin but it also includes some treated with 30 mg. doses, which were used in only a few of the second group and in none of the first.

These observations suggest that the milder the frostbite the more efficacious heparin therapy may be expected to be, and vice versa, and that the more prolonged the coagulation time the greater the efficacy of anticoagulant

therapy in preventing gangrene. They suggest also that such treatment may be futile unless it is begun promptly after freezing. They demonstrate conclusively two facts: first, that heparin therapy is of some efficacy in preventing or limiting in extent and degree the gangrene of experimental frostbite, and second, that this therapy is not as uniformly successful as has been reported by others.

The careful pathologic studies of Friedman, Lange, and Weiner failed to demonstrate any significant nerve damage in frostbitten rabbits adequately treated with heparin. In the experiments of Lange and Boyd and in our own, sensory loss followed frostbite even when gangrene was averted by use of anticoagulant therapy. In contrast, when the circulation to the foot was completely shut off by tourniquet for periods equal to or greater than those of the exposure, no sensory loss followed. This would suggest that cold itself may bring about at least a functional alteration of the nerves.

The studies reported confirm the plausibility of the important suggestions of Brambel and Loker and of Lange and his co-workers that the use of anticoagulant therapy should be investigated in clinical cases of injury due to cold, and that this therapy may be expected to be a valuable aid in the management of such problems. They would lead one to believe that this treatment cannot be expected to avert gangrene in every instance. It should be pointed out, to be sure, that frostbite in man is often less severe than that utilized in this experimental study. On the other hand, patients with frostbite are often not available for treatment as soon after injury as was practiced in our investigation. Furthermore, heparin cannot be given to man in near fatal amounts as we have done in our experiments. The ultimate usefulness of anticoagulant therapy in human injuries due to cold must await clinical trial. Because in animal experimentation alone the various related factors can be adequately controlled, however, it may be anticipated that many important observations concerning the problem of anticoagulants in frostbite will necessarily depend upon such investigations.

CONCLUSIONS

Adequate heparinization is a valuable but not an invariably reliable therapeutic aid in the prevention or limitation in extent and degree of gangrene in experimental frostbite in rabbits.

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THE USE OF ANTICOAGULANTS IN THE SURGERY OF ANEURYSMS AND ARTERIOVENOUS FISTULAS, WITH PARTICULAR REFERENCE TO DICUMAROL

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DURING the recent war an opportunity at one of the Vascular Centers was afforded us to study the clinical applicability of anticoagulant therapy in vascular surgery. The clinical material consisted of a group of patients in whom some type of reparative or restorative procedure had been employed in an effort to maintain the continuity of the affected artery following surgical obliteration of a peripheral aneurysm or arteriovenous fistula. Heparin and dicumarol were used either alone or together.

Since the reported experimental and clinical data regarding anticoagulant therapy in arterial surgery are limited to the use of heparin alone,[1, 2] it was felt advisable to present our experiences. Furthermore, it was hoped that it would be helpful to record the methods and means of control of the therapy employed, to discuss the general results and complications encountered, and to demonstrate that reparative surgery of the peripheral arteries can be safely accomplished with anticoagulants given at the time of operation or before. The material was insufficiently controlled, however, to warrant drawing definite conclusions concerning the efficacy of anticoagulants in the prevention of thrombosis following arterial repair.

CLINICAL MATERIAL AND METHODS

Some type of reparative procedure was performed in 34 of 290 aneurysms and arteriovenous fistulas treated surgically,[3] and of this number 22 patients were given anticoagulant therapy for a more or less prolonged period of time. An additional patient received a single injection of heparin. The basis for the selection of cases for repair and the clinical results have been presented elsewhere.[4] The methods employed for preserving the continuity of the vessel consisted of ligation and transfixion of the fistula, lateral arteriorrhaphy, resection of a segment of artery with end-to-end suture, and vein transplantation. Anticoagulant therapy was used infrequently with the first method, generally with the second, and routinely with the other two (Table I).

Crystalline heparin in aqueous solution was administered every four hours by the intravenous route, in 50 mg. doses. The first injection was given at the time of operation as soon as the decision was made to attempt arterial repair. In general, it was utilized only during the initial period of dicumarol therapy until a satisfactory alteration of prothrombin level had been obtained with

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TABLE I. RESULTS IN CASE OF ARTERIAL REPAIR

TYPE OF REPAIR	NO. OF CASES	NO. RECEIVING ANTICOAGULANTS	NO. OF CASES IN WHICH THROMBOSIS OCCURRED
Transfixion of fistula	13	4*	0
Lateral arteriorrhaphy	5	3	1
End-to-end suture	10	10	2
Vein transplantation	6	6	1

*One of these patients received only a single 50 mg. dose of heparin.

the latter. The anticoagulant effect was measured occasionally but not regularly by clotting time determinations carried out according to the method of Lee and White.[5]

Dicumarol was administered to any given patient only after an initial prothrombin level had been obtained. In general, 300 mg. were given the first day, 200 mg. the second day, and 100 mg. on the third day. Thereafter the dosage was determined on the basis of the level of the daily prothrombin time. The exact quantity required to maintain the prothrombin time at the desired level varied for the different patients and not infrequently for the same patient during the course of therapy. Generally a daily dose of 100 mg. was necessary, although in some instances smaller amounts were adequate. When patients were being given heparin and dicumarol concurrently, blood for prothrombin determinations was drawn just before the administration of a dose of heparin in order to minimize any possible effect of the latter upon the prothrombin blood level determination. It was found to be a safeguard to delegate the dicumarol therapy to one member of the staff who received a report of the prothrombin determinations each morning and then gave necessary orders with regard to dosage. An effort was made to maintain the prothrombin level around 20 to 30 per cent of normal according to the Quick curve[6]; this is roughly equivalent to a "clotting index" of 50.

The method of Quick[7] was used for the determination of prothrombin time. Four and one-half cubic centimeters of blood were withdrawn by venopuncture and placed in a test tube containing 0.5 c.c. of 1.3 per cent sodium oxalate. The contents of the tube were well mixed and then centrifuged. Three Loeffler test tubes, into each of which 0.1 c.c. of the plasma was introduced, were placed in a water bath kept at from 35° to 40° C. One-tenth cubic centimeter of thromboplastin,* previously brought to the same temperature, was added to each tube, being blown from a pipette so as to bring about immediate mixing. One-tenth cubic centimeter of calcium chloride was then quickly blown from a pipette into each of the test tubes and simultaneously a stop watch was started. After a short interval one of the tubes was removed from the bath, held up against a light, and tilted back and forth until clotting took place; the end point was considered to be the time at which the particles of thromboplastin ceased moving while the plasma continued to do so. Care was taken to avoid marked agitation of the contents of the tube. The watch was stopped and read at the moment clotting was noted. Two of the test tubes were used for preliminary guide

*The thromboplastin was obtained as Bacto-Thromboplastin from the Difco Laboratories, Incorporated, Detroit, Mich., or was prepared in the laboratory from rabbit brain.

readings and the third for more precise determination of the clotting time. A control test with normal plasma was run with each daily set of determinations. Values were expressed in per cent of normal, utilizing the curve developed by Quick.[6]

RESULTS

The method of administration of anticoagulants varied in the different cases. In 18 patients combined heparin and dicumarol therapy was utilized. The operative procedure carried out in this group consisted of ligation and transfixion of the fistula in 1 instance, lateral arteriorrhaphy in 3, end-to-end suture in 10, and vein transplantation in 4. The heparin was begun at the time of operation and administered in 50 mg. doses at four-hour intervals for an average of two days. The dicumarol was started as soon after operation as a prothrombin determination could be obtained, and in most instances it was continued for a period of three weeks. In a few cases it was given only for a period of from ten to sixteen days, while in 4 it was used for an even shorter period of time. In one of the latter it was discontinued after six days because of an unusually marked response resulting in a very low prothrombin level. In another, in whom a lateral suture had been performed in the presence of gross infection, dicumarol was stopped after the third day, while in the third it was not given after the fourth day because of persistent bleeding from the wound.

The fourth case in the group receiving dicumarol for a short period of time deserves more detailed presentation. In this instance, in which a brachial aneurysm was excised and an end-to-end suture accomplished, heparin was started at the time of operation and dicumarol was administered shortly afterward. Through an error the patient received 300 mg. of dicumarol every four hours for five doses, in addition to 50 mg. of heparin every four hours during the same period of time. When the mistake was recognized, all anticoagulant therapy was stopped and 60 mg. of synthetic vitamin K were administered intravenously. The prothrombin level remained fairly low for several days but not alarmingly so and no hemorrhagic difficulties ensued.

In four cases dicumarol was given before and an adequate reduction in prothrombin level had already been attained at the time of surgery. Two of these patients, in whom vein transplantation was performed, also received a single dose of heparin during the operation, while in the other two, in whom a fistula was transfixed and the vein divided, no anticoagulant other than dicumarol was utilized. In all four, dicumarol was continued for a period of approximately three weeks. The last patient in the series received no anticoagulant treatment other than a single dose of heparin given at the time of operation.

Three patients developed thrombosis despite the use of anticoagulants (Table II). In two of these a traumatic aneurysm of the distal end of the brachial artery existed, and in both it was possible to resect the aneurysm and perform an end-to-end suture. The proximal end of the artery sutured was perfectly normal but in each instance the distal portion was somewhat scarred. However, further resection back to more normal-appearing vessel wall was prohibited by the proximity of the point of bifurcation. In one of these patients

TABLE II. CASES IN WHICH THROMBOSIS OCCURRED

CASE NO.	TYPE AND LOCATION OF LESION	TYPE OF REPAIR	ANTICOAGULANT THERAPY	PROBABLE CAUSE OF THROMBOSIS
1	Femoral A-V fistula	Lateral arteriorrhaphy	None	Local damage to artery; operative constriction of lumen
2	Brachial aneurysm	End-to-end suture	Heparin,* dicumarol	Local damage of artery
3	Brachial aneurysm	End-to-end suture	Heparin, 2 days; dicumarol, 2 weeks	Local damage of artery
4	Brachial aneurysm	Vein graft	Heparin, 50 mg.; dicumarol, 2 weeks	Questionably imperfect suture due to small caliber of lumen

*Through error this patient received 200 mg. of heparin and 1,500 mg of dicumarol during the first seventeen hours after operation. Anticoagulants were stopped at this time and 60 mg. of synthetic vitamin K were given.

heparin was administered immediately after operation and dicumarol was continued for two weeks. The other was one referred to previously in whom a very large amount of dicumarol was given erroneously during the first twenty hours postoperatively, after which all anticoagulant therapy was discontinued. In both, thrombosis could reasonably have been attributed to the local arterial damage. The third patient was one in whom a brachial aneurysm was excised and a vein graft was performed. An adequate prothrombin level had already been achieved with dicumarol at the time of operation. A single dose of heparin was given during the surgical procedure and dicumarol was continued for about two weeks. No explanation for the cause of thrombosis is evident, although it is not unlikely that an imperfect suture may have been performed because of the unusually small size of the artery, even though the completed anastomosis appeared satisfactory at the time of operation. It is important to point out that there was no evidence of propagation of a clot in any of the 3 cases in which thrombosis of the repaired segment occurred.

In no case in the series of patients receiving anticoagulants was any particular difficulty with hemostasis experienced at operation, regardless of whether heparin was given immediately before the anastomosis was accomplished, or whether the prothrombin time had been altered beforehand through the administration of dicumarol. As a safeguard, fibrin foam was often placed in the wound, a precaution which appeared to give some protection against bleeding from the operative site without adding any risk of intravascular clotting.

In several cases some later difficulties with bleeding were encountered. One patient, who had a lateral suture of the subclavian artery and who was receiving dicumarol, developed a hematoma of moderate size in the wound. The operative site was explored on the tenth day and a clot was evacuated. No bleeding was encountered and the wound was closed; convalescence was uneventful. Another patient, upon whom a vein graft to the popliteal artery had been performed, had a small hematoma which was evacuated without difficulty in bed. He had no further bleeding during the six weeks' period in which dicumarol was administered. A third patient had developed a large hematoma

shortly after excision of a femoral arteriovenous fistula and vein transplantation. The wound was re-explored two hours after operation and brisk bleeding from a small muscle branch was found. This artery was ligated, the wound was closed, and no further difficulty ensued, although dicumarol was continued for several weeks.

In a fourth patient a slow, steady oozing of bright blood from the wound was noted shortly after a femoral arteriovenous fistula had been excised and a vein graft performed. In spite of this bleeding, heparin was continued intermittently until an adequate prothrombin level had been obtained with dicumarol. On the fourth day the dicumarol was stopped, since by this time blood loss had been sufficient to result in a significantly lowered erythrocyte count. The patient was given 50 mg. of synthetic vitamin K and a transfusion of whole blood, and the wound was explored. Only diffuse capillary bleeding was found, the wound was closed, and no further bleeding took place. In none of these patients did thrombosis of the repaired segment take place.

In another instance the brachial artery remained patent after lateral suture in the presence of gross infection. However, hemorrhage occurred through the unhealed suture line on the thirteenth postoperative day, and as a result excision of the segment had to be carried out. Since dicumarol had been discontinued ten days before the bleeding took place, it seems unlikely that this agent was implicated in the untoward response, but rather that it was due to the nonhealing consequent to the infection.

It is of interest to discuss some of the findings in the 11 of the 34 patients in the series in whom anticoagulant therapy was not utilized. In one a femoral arteriovenous fistula was resected and the rent in the artery was repaired by a lateral suture. There was obvious injury to the artery wall in the neighborhood of the fistula and the vessel was constricted to about one-half of its diameter by the suture. It appeared doubtful that the procedure would be successful at the time of operation but it was decided to do nothing further since blood flowed freely through the segment. Two hours after operation it was apparent from the absence of pulses in the popliteal, dorsal pedal, and posterior tibial arteries that thrombosis had occurred. The wound was re-explored and a thrombus was found sharply limited to the repaired segment of the artery and without proximal or distal propagation. It was excised and the artery was ligated. In retrospect it would seem that the segment should have been excised originally and a vein transplantation performed. It also would have been wise to have used anticoagulants.

In another patient, in whom a fistula was ligated and transfixed, the only instance in which this procedure was not supplemented by division of the vein and use of the cuff of vein for buttressing the ligated fistula, a prompt recurrence took place. This necessitated subsequent excision and quadruple ligation of the vessels. In the remaining 9 patients in this group, thrombosis did not occur and no other untoward results were observed.

Of the series as a whole, in 28 cases the arterial reparative procedure was entirely successful, since the patency of the repaired segment was subsequently

evident from various observations and tests. In the remaining 6 instances, described previously, in which the results locally were not satisfactory, no gross impairment of circulation to the extremity followed.

DISCUSSION

The clinical applicability of anticoagulant therapy in operative cases is being more precisely defined as a broader experience is being obtained. It is becoming evident that the desired anticoagulant effect is hazardous during certain operations within the abdomen, thorax, and cranial cavity, where postoperative bleeding may be unrecognized until the patient's life is in jeopardy and where control of hemorrhage is difficult. In such cases it is necessary to delay the use of anticoagulants until sometime postoperatively and then only in cases in which it can be reliably assumed that all bleeding has ceased. Certain operations upon bones and joints fall into the same category. On the other hand, the present report demonstrates that surgery of the peripheral arteries can be undertaken at a time when a full anticoagulant effect has already been obtained either from dicumarol or heparin. One must be sure, however, that adequate hemostasis has been achieved before the wound is closed. Fibrin foam seems to be helpful in regard to control of capillary bleeding and undoubtedly certain other coagulant sponges would be similarly useful. Despite such precautions, it appears reasonable to assume that the use of anticoagulants will result in an increase in the incidence of hematoma and in persistent oozing of wounds. Nevertheless, the possible dangers of such complications are minimal if they are recognized promptly and are treated properly by surgery if indicated, by cessation of anticoagulant therapy, and by the use of reversing agents such as synthetic vitamin K.

The efficacy of heparin in preventing thrombosis in cases of arterial repair is suggested both by experimental and by clinical observations.[1, 2] That dicumarol is of benefit in reducing the incidence of postoperative venous thrombosis and pulmonary embolism is also indicated by the good results which have been obtined by us and by others in clinical cases.[8, 9] On the basis of such experiences, it would seem likely that dicumarol should also be effective in reducing the incidence of thrombosis after arterial repair. However, the present report does not furnish complete proof of such efficiency, since no comparable group of patients was treated without anticoagulants and since most of our patients received heparin as well as dicumarol. The 11 cases in the series in which this therapy was not utilized cannot serve as proper controls, since most of them are patients upon whom the simpler types of reparative surgery were performed, while anticoagulants were generally reserved for those in whom the type of repair was such that the hazard of thrombosis was greater. Nor can untreated cases from the literature be used for this purpose since so many other factors are important in the success of arterial surgery as, for example, the type of repair, the proficiency of the operator, the presence or absence of infection, and the degree and extent of the local arterial injury or disease. It is our impression, nevertheless, that dicumarol and heparin were of benefit in preventing arterial thrombosis in the present series. That they are not

a complete safeguard is suggested by the finding that an adequate and prolonged anticoagulant effect did not prevent thrombosis in two of our patients. It appears evident that, helpful as anticoagulants may be, they will not assure success unless the local damage to the sutured artery is not great and unless the surgical repair is properly performed.

It is of interest that in none of the 4 cases of thrombosis was there evidence of extension of the clot from the repaired segment. That the maintenance of good blood flow in the distal segment through adequate collateral channels is important in this regard is evidenced by the fact that there was no propagation of thrombus in the one instance in which anticoagulants were not used as well as in the 3 in which they were. Nevertheless, it is reasonable to assume that anticoagulant therapy will also prove of aid in this important problem of prevention of distal extension of the clot.

Up to this point we have discussed the use of anticoagulants only in those cases in which some reparative procedure was carried out. It is appropriate to inquire into its possible usefulness in patients in whom the affected artery is not repaired but is ligated and divided. We did not use anticoagulants in this series and only in 2 of the 256 cases[3] did postoperative thrombosis occur. A nonfatal partial hemiplegia presumably due to distal propagation of thrombus developed in one patient some hours following ligation of the internal carotid artery for an intracranial carotid aneurysm. In the other instance, a disaster of such moment took place that it appears of interest to present a detailed account of the occurrence.

The patient had a femoral arteriovenous fistula, just distal to the point at which the profunda was given off, which necessitated excision and quadruple ligation of the vessels. The foot maintained good circulation until the sixth postoperative day when the patient suddenly developed intense pain in the calf and foot, followed by swelling of the leg, and coldness, pallor, and numbness of the foot. On examination it was evident that extensive venous and arterial thrombosis had occurred. In spite of a poor temperature and color response to spinal anesthesia, sympathectomy was performed as a last resort. The warmth and sensation of the foot were actually improved significantly by this procedure, although the increase in circulation was insufficient to prevent gangrene of the sole of the foot, subsequently necessitating amputation. Anticoagulants were begun shortly after the difficulty was first noted, without any apparent therapeutic effect.

Although this is the only case in a large experience in which postoperative thrombosis occurred in an extremity, it makes one wonder whether the routine use of anticoagulants in the surgery of peripheral aneurysms and fistulas might not be valuable in avoiding such rare but disastrous occurrences. Such a program would undoubtedly result in a higher incidence of hematomas of wounds, but, as has already been pointed out, one would not expect such difficulties to be serious.* However, the advisability of the routine use of anticoagulants in

*One of us (H.B.S.,Jr.) has subsequently utilized dicumarol with good therapeutic results in a patient before and after aneurysmorrhaphy for an arteriosclerotic popliteal aneurysm. The distal portion of the artery had undergone thrombosis several days before operation.

the surgery of peripheral aneurysms and fistulas will necessarily depend upon the results obtained after an extensive clinical trial.

With regard to selection of the anticoagulant agent or agents to be used, it is apparent that dicumarol has advantages over heparin in cost and in ease of administration in those institutions in which it is economically feasible to provide facilities for accurate daily determinations of blood prothrombin. However, if these are not available, the drug should never be used, for its uncontrolled administration is fraught with great danger. Under such circumstances heparin can be employed more safely. From our clinical experience it would seem preferable to obtain adequate prothrombin levels preoperatively, using dicumarol, rather than to begin anticoagulant therapy with heparin at the time of the surgical procedure. With this type of program, one can avoid the necessity of intravenous administration of heparin during the first few days after operation. It must be pointed out, however, that our studies throw no conclusive light upon the relative merits of dicumarol and heparin in the prevention of arterial thrombosis. Although we have the impression that anticoagulant therapy played a role in the good results obtained with various methods of arterial repair, as we have mentioned previously, our cases are not adequately controlled from this viewpoint. Furthermore, in all but a few of our patients both heparin and dicumarol were given, although heparin therapy was generally of short and dicumarol therapy of long duration. The recent experiments of Kiesewetter and Shumacker[10] demonstrate that thrombosis is apt to occur early after arterial trauma, and hence the most critical period is that immediately following operation. It is obvious that the elucidation of the entire problem of the relative worth of dicumarol and heparin in vascular surgery must await further extensive experimental and clinical trial. It is of interest that recent studies in which the two drugs were compared under controlled conditions[10] suggest that heparin is more effective than dicumarol in the prevention of thrombosis after arterial injury and repair. In the light of these experiments and our clinical experience, it is suggested that use of both heparin and dicumarol may be the most effective means of carrying out anticoagulant therapy as an adjuvant in the surgery of peripheral arteries. It would appear advisable to use heparin at the time of the operation and for the first five or six days thereafter, perhaps preferably combined with dicumarol therapy, and to continue administration of dicumarol during the following week or two.

CONCLUSIONS

1. Experiences are recorded with the use of anticoagulants and particularly of dicumarol in cases of reparative arterial surgery for aneurysms and arteriovenous fistulas.

2. The methods of administration and of control are discussed as well as the complications which may result from such therapy.

3. The study presented indicates that reparative procedures upon peripheral arteries can be safely undertaken when a full anticoagulant effect has been achieved with heparin, dicumarol, or both.

4. Although no proof of the effectiveness of anticoagulants has been furnished, suggestive evidence has been obtained for the belief that such therapy renders less likely thrombosis of the repaired segment of artery.

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PULMONARY ARTERIOVENOUS ANEURYSM

A New Surgical Disease

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THE great English anatomist, William Hunter (1718-1783), brother of John Hunter, was first (1761) to describe an arteriovenous aneurysm as "The simultaneous rupture of an artery and a vein in which the blood flows directly into a neighboring vein (aneurysmal varix), or else is carried into such a vein by a connecting sac (varicose aneurysm)."

To date the medical literature contains reports of only ten cases of congenital or nontraumatic pulmonary arteriovenous aneurysm. The lesions have been reported under various titles; such as, cavernous hemangioma of lung (seven cases), multiple pulmonary hemangiomas (one case), arteriovenous fistula of lung (two cases). As the gross anatomy in each case is identical and consists of a lobulated, thin-walled, branching, blood-filled pulsating pulmonary sac of varying size made up of both an arterial and a venous component, it seems more accurate and logical to call these lesions pulmonary arteriovenous aneurysms in order to distinguish them from (a) benign hemangioma of the lung, (b) metastatic pulmonary hemangioma of the lung, or (c) hemangioendiothelioma of the lung.

Pulmonary arteriovenous aneurysm is truly a rare condition and no account of such a lesion is to be found in the group of world reports of large series of routine autopsies. The first unquestioned case appears to be that reported by Rodes in June, 1938.[10]

As the symptom complex is so definite and typical as to be easily recognized, and cases are being more frequently reported of late, it is possible that patients with this disease in the past masqueraded under the erroneous diagnosis of congenital heart disease or polycythemia vera.

A pulmonary arteriovenous aneurysm produces in the lung a shunt whereby a considerable amount of blood passes from the arterial to the venous circulations of the pulmonary circuit without passing through the alveoli of the lung to be oxygenated. The physiologic effect of this is to produce a low oxygen saturation of the arterial blood supply, and all the other changes are secondary to this anoxemia.

The extreme rarity of this congenital defect lends zest to a desire for discovering and reporting examples of it. In addition, a patient so afflicted is in constant danger of hemorrhage which sometimes is copious and fatal, and cerebral thrombosis with epileptiform seizures due to the slowed circulation and increased red blood cell volume is to be feared. Coronary artery thrombosis also is known to occur. A mild degree of invalidism necessitating curtailment of normal activities is usual, and occasionally venesection and hospitalization are required.

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TABLE I. ANALYSIS OF TWELVE CASES OF

AUTHOR	AGE (YEARS)	SEX	SIGNS AND SYMPTOMS: EPILEPTIFORM ATTACKS	EXERTIONAL DYSPNEA	CYANOSIS	HEMORRHAGE	TRAUMA	CLUBBING OF FINGERS AND TOES	HEMANGIOMAS OR PETECHIA	BRUIT OR HEART MURMUR	LUNG INVOLVED	HEART NORMAL	RADIOGRAPH, TOMOGRAPH, ANGIOCARDIOGRAPH
1. Bowers, 1936	2 days	M	0	0	0	+	0	0	+	0	Left	+	0
2. Rodes, 1938	25	M	+ (6)	+	+	+ (3)	0	+	+	0	R.M.L., and L.U.L.	+	+
3. Smith & Horton, 1939	40	M	+	+	+	0	0	+	0	+	Rt.	+	+
4. Hepburn & Dauphinee, 1942	23	F	+	+	+	0	0	+	0	0	Rt.	+	+
5. Goldman, 1943	22	M	0	+	+	0	0	+	+	0	Left	+	+
6. Jones & Thompson, 1944	24	F	0	0	+	0	0	+	0	+	R.U.L.	+	+
7. Janes, 1944	30	M	0	0	+	+ (5)	0	0	+	+	Both	+	+
8. Adams & associates, 1944	24	M	0	0	+	Epistaxis	0	+	+	0	Left	+	+
9. Alexander, 1945	41	M	+ (1)	+	+	0	+	+	+	+	Left & right, multiple	?	+
10. Makler & Zion, 1946	17	M	0	+	+	Epistaxis	0	+	0	+	Both	+	+
11. Watson, 1947	27	M	0	0	+	0	0	0	0	0	Rt.	+	+
12. Watson, 1947	21	M	+ (1)	+	+	+	0	+	+	0	Rt.	+	+

The importance of an early diagnosis becomes obvious when one finds that six patients have been cured by surgical measures. Two of these surgical results form the basis of this report. Surgical measures varying in magnitude from pneumonectomy, lobectomy, and multiple local excisions, to ligation of the offending or "feeder" artery have been carried out, and there have been no postoperative fatalities reported. The patients in each case have returned to their usual occupations. The untreated or medically managed patients have not improved, or have died of the complications of their disease.

DIAGNOSIS

If one bears in mind the possibility of pulmonary arteriovenous aneurysm, the diagnosis can certainly be established before operation. The reported ages vary from 2 days to 41 years. However, all but three patients were between the ages of 17 and 30 years. The ratio of the sexes is ten males and two females. Persistent cyanosis of the face, hands, and feet was noted in ten cases and absent in two. Clubbing of the fingers and toes was noted in nine cases

PULMONARY ARTERIOVENOUS ANEURYSM

					TREATMENT							
R.B.C. (IN MILLIONS)	HEMATOCRIT (PER CENT)	HEMOGLOBIN	W.B.C. (IN THOUSANDS)	PLATELET COUNT	VENESECTION	PHENYLHYDRAZINE	RADIATION THERAPY	PNEUMOTHORAX	T. B. TREATMENT	MEDICAL TREATMENT ONLY	SURGICAL CARE	RESULT
0	0	0	0	0	0	0	0	0	0	+	0	Died
7.5	0	113%	9.8	0	0	0	0	0	0	+	0	Died of third hemorrhage
6.2	66	23.7 Gm.	3.2	0	Numerous	+	0	0	0	+	0	Living
9.6	0	21.8 Gm.	0	Normal	0	0	0	+	+	0	Pneumonectomy	Cured
11.4	0	137%	4.1	855,000	0	0	0	0	0	+	0	Unimproved
7.5	0	130%	Normal	Normal	0	0	+	+	0	0	Pneumonectomy	Cured
0	0	0	11.4	0	0	0	0	0	0	0	Multiple local resections	Improved
7.2	82	23 Gm.	6.6	0	750 c.c. preop.	0	0	0	0	0	Pneumonectomy	Cured
8.5	0	20.4 Gm.	7.6	0	+	+	+	0	0	+	0	Died, coronary thrombosis
7.7	55	19.5 Gm.	6.5	175,000	0	0	0	0	0	+	0	Unchanged
Normal	Normal	Normal	Normal	Normal	0	0	0	0	0	0	Ligation "feeder" artery	Improved
6.5	58	17 Gm.	6.0	110,000	Several 1000 c.c.	0	0	0	0	0	Lobectomy	Cured

and absent in three. A high red blood cell count, ranging from 6 to 11.4 million, was noted in all but one case (in two cases the red blood cell count is not reported). The hemoglobin varied from 17 to 23.7 Gm., and the hematocrit from 55 to 82 per cent. The white blood cell count was normal in each case. The heart was normal in all cases, and the electrocardiographic tracings and blood pressure readings, when done, were not significant. Half the patients reported exertional dyspnea.

Radiographic studies were of great diagnostic value. In each case a branching, lobulated mass of uniform density was noted in the lung field and confirmed by tomographic and, or, angiocardiographic studies whenever these were done.

Other diagnostic features were hemorrhage, epileptiform seizures, bruit or heart murmur, a normal platelet count, a normal spleen, and normal sternal puncture studies. There was occasionally a history of cough and persistent headaches. In only one case was there a history of trauma (Table I).

TREATMENT

Various medical measures have been employed in the past in the management of pulmonary arteriovenous aneurysm: (1) Repeated venesections varying in amount up to 1000 c.c. brought about temporary symptomatic improvement in four cases. (2) Phenylhydrazine was used and afforded two patients temporary relief. (3) Artificial pneumothorax was instituted in two cases, but the patients were not improved. (4) One patient was given a trial of tuberculosis sanatorium regime without success. (5) Radiation therapy was of no value in two cases. (6) Surgical care was given six patients; in three instances pneumonectomy resulted in cure, one patient was apparently cured by lobectomy, another by multiple local excisions, and in another patient the feeder artery to the arteriovenous aneurysm was isolated and cut between ligatures. This patient had no symptoms and returned to his usual occupation, but needs observation over a period of years to evaluate the result. The procedure in this case was suggested to me by a remark made by Dr. I. A. Bigger in discussing the case of arteriovenous aneurysm reported by Jones and Thompson.[6] He asked the question whether simple ligation of the responsible artery would not be enough to cure the condition. This case may give us some clue to the answer.

DIFFERENTIAL DIAGNOSIS

Polycythemia vera can be ruled out by the age of the patient, the lack of splenomegaly, the normal range of the white blood cell and platelet counts, and the lack of hyperplasia of the white cell progenitors and megakaryocytes in the bone marrow. Secondary polycythemia due to high altitude, or poisoning by heavy metals or aniline dyes, can be ruled out by the history alone, and cardiac anomalies, with a right to left shunt or chronic pulmonary disease preventing adequate oxygenation, may be ruled out by the roentgenographic and electrocardiographic findings.

PROGNOSIS

As pointed out by Makler and Zion,[9] the prognosis must be accepted as grave with the danger of massive hemorrhage always present. If untreated, the secondary polycythemia will lead to serious complications, namely, exhaustion of the bone marrow with anemia, granulocytopenia, and thrombocytopenia (Table II).

Thrombosis is a real danger due to the increased viscosity of the blood, the increased cell mass, the slowing of the circulation, and the tendency to clot.

TABLE II. PROGNOSIS*

1. Exhaustion of bone marrow leading to anemia, granulocytopenia, thrombocytopenia
2. Thrombosis—cerebral and coronary
3. Hemorrhage—six cases, two deaths
4. Duodenal ulcer
5. Six patients well after surgical treatment

*A good prognosis seems indicated by the surgical reports to date.

Theoretically at least, the altered blood factors would tend to place an abnormal burden on the heart.

Duodenal ulcer is found commonly in patients with polycythemia and is said to be due to vascular changes leading to a plugging of small vessels in the intestinal wall.

Half the patients have been treated surgically with excellent immediate results.

Fig. 1.—Case 1. C. E. Chest radiograph showing the lobulated branching density in the right lower lobe.

CASE REPORTS

CASE 1.— C. E., a 27-year-old Private First Class, U.S.M.C.R., was due for discharge from the service in September, 1945. At that time a routine separation radiograph of the chest revealed a peculiar shadow in the right lower lung field. He had no symptoms and radiographs taken eighteen months previously were said to be negative.

The patient's family history was not remarkable except for the death of his mother at the age of 29 of pulmonary tuberculosis. Past history revealed that he had smoked heavily, taken alcohol in moderation, and had suffered two attacks of benign malaria. There was one questionable hemoptysis in 1945.

The patient, a short, heavy, solidly built man weighing 185 pounds appeared normal and healthy. The skin revealed a severe acne vulgaris which was most marked on the back, and there was also a diffuse folliculitis of the anterior part of the chest wall. The heart and lung sounds were normal, the pulse rate 78, and the blood pressure 130/86. Laboratory studies were essentially normal, as shown in Table I, Case 11.

Chest radiographs taken Sept. 5, 1945, showed several circular and elliptical densities in the right lower lobe measuring from 2 to 3½ cm. in size (Fig. 1). Bronchograms ruled out bronchiectasis and the roentgenologist suggested a diagnosis of lung cyst.

Aspiration biopsy and bronchoscopy did not add definite information. The spirogram and vital capacity studies were normal, and the medical evaluation for surgery was reported as good.

Operation was carried out Feb. 28, 1946. The right side of the chest was opened through the bed of the partially resected sixth rib. The right lower lobe was found to be adherent to the chest wall and diaphragm by old fibrous adhesions. In the substance of the right lower lobe, there was a soft lobulated, compressible mass about 4 cm. in diameter which pulsated and transmitted a thrill to the fingers (Fig. 2). Entering the posterior costophrenic edge of the lobe, there was an aberrant artery ½ cm. in diameter. When this vessel was compressed the pulsating mass in the lung was no longer palpable. The artery was then followed to its origin from the thoracic aorta, doubly ligated, and cut across. The lung was then expanded and appeared to be normal. Because the mass could not be palpated and it was believed that the feeder artery had been severed, it was decided that lobectomy was not necessary.

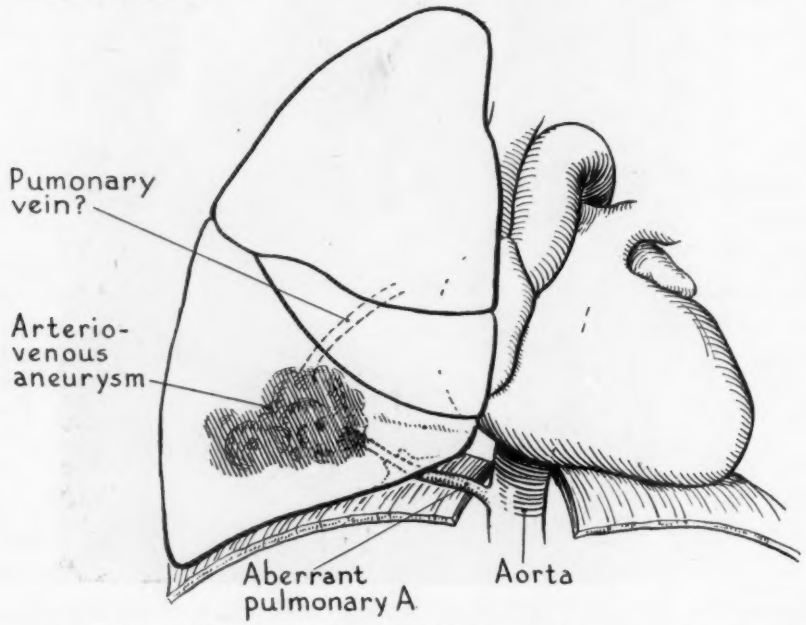

Fig. 2.—Case 1. C. E. Sketch showing the arteriovenous aneurysm. The aberrant artery was doubly ligated and severed near its origin from the aorta.

The postoperative course was complicated by severe diarrhea and persistent abdominal distention. Suppuration occurred in the central portion of the wound, probably because of our inability to control preoperatively the severe acne and folliculitis. Culture showed *Staphylococcus aureus* hemolyticus.

The patient was surveyed from the Naval Service and at the time of this communication was again without symptoms, working at his usual employment. Following operation, checkup radiographs revealed the right lower lobe to be unchanged, and only on serial films over a long period of time will we be able to learn what has happened to the stagnant blood in the spaces supplied by the ligated aberrant artery.

CASE 2.—R. G., a 21-year-old Private First Class, U.S.M.C.R., was first admitted to the sick list on August 30, 1945, complaining of dusky color of skin and fingernails of at least one and one-half years' duration, shortness of breath on mild exercise for six months, frequent headaches, weight loss of thirty pounds in two years, bleeding gums, and prickly warm feeling over entire body.

The patient's parents, two brothers, and one sister were living and well, and there was no familial disease. The father stated that the patient had always had a "dusky" color compared with his other children.

The patient's past history was not remarkable. Specifically, he never had scarlet or rheumatic fever, nor other serious illnesses, and had never been operated upon. His early life was spent in Denver, Colo., at an altitude of 5,000 feet. He had thirty-three months' active duty in the Marine Corps, with fifteen months overseas. A review of the photofluoroscopic film taken at the time of induction in January, 1943, revealed the pulmonary lesion.

Fig. 3.—Case 2. R. G. Angiocardiograph showing the vascular anomaly in the right lower lobe.

The patient, a tall, well-built, plethoric man, showed marked cyanosis, especially of the lips and face. The retinal vessels were tortuous without evidence of hemorrhage. One small pinhead sized hemangioma was noted in the conjunctiva of the left lower eyelid. Similar hemangiomas were found in the vermilion border of the lower lip, the tip and lateral borders of the tongue, in the bed of one fingernail, and in the palms of both hands.

Heart sounds were normal, with a blood pressure of 110/70 and a pulse rate of 72. The lungs seemed clear to percussion and auscultation. The spleen and liver were not palpably enlarged.

Laboratory data revealed red blood cells, 6,500,000; white blood cells, 6,000 with normal differential; hemoglobin, 17 Gm.; sedimentation rate, 2. mm. –1 hr.; hematocrit, 58; bleeding

TABLE III. LUNG FUNCTION STUDIES SHOWING ARTERIAL OXYGEN CHANGES AFTER LOBECTOMY*

ARTERIAL OXYGEN	REST	AFTER MODERATE EXERCISE
	Before Operation	
Content vol. per cent	23.1	21.3
Capacity vol. per cent	25.8	26.7
Saturation per cent	90	80
	After Operation	
Content vol. per cent	16.8	16.3
Capacity vol. per cent	17.5	18.1
Saturation per cent	95.4	91.0

*Case 2, R. G.—The oxygen saturation has increased to 95.4 per cent.

time, 1 min. 45 sec.; clotting time, 3 min. 15 sec.; reticulocytes, 0.6 per cent; platelet count, 110,000; icterus index, 4 units; CO_2 combining power, 58 per cent; Kahn reaction, negative; urinalysis, normal; tuberculin test, 1-10,000, negative; sternal puncture studies, normal type of bone marrow (2 examinations); electrocardiogram, normal.

The patient was hospitalized and studied for twelve months. Temporary, symptomatic relief was obtained several times by phlebotomy of 1000 c.c. On Jan. 13, 1946, he suddenly had a tonic convulsion with transient coma and paralysis of the left arm and leg. Symptomatic treatment was followed by a gradual return of muscular activity and control, leaving a residual hypesthesia of the left leg.

Bronchoscopy and bronchography were helpful in eliminating the possibility of a bronchial disorder. Angiocardiography was done on April 12, 1946, at Mount Sinai Hospital. After the intravenous injection of 70 per cent diodrast, roentgenograms were taken and reported as follows. There was a collection of wide vascular channels in the right lower lobe which formed a racemose grouping. The maximum opacity occurred at about four seconds after injection, which would suggest that these channels were probably venous in nature, but there was the possibility of an arteriovenous communication. The main pulmonary artery was normal in size as was the left pulmonary branch. The right pulmonary artery was relatively large. This vascular anomaly was in the right lower lobe (Fig. 3).

The lung function unit of the chest service, Columbia University, Division of Bellevue Hospital carried out detailed blood volume and oxygen saturation studies prior to and after operation. These findings are summarized in Table III and IV.

Operation was done Aug. 8, 1946, under intratracheal gas, oxygen, and ether anesthesia. A right posterolateral incision was made and the chest opened through the bed of the partially resected sixth rib. There was no free pleural space to be found because the parietal and visceral pleuras were sealed to each other by a sheet of old dense adhesions

TABLE IV. LUNG FUNCTION STUDIES SHOWING POSTOPERATIVE IMPROVEMENT IN BLOOD FACTOR*

	BEFORE OPERATION	AFTER OPERATION
Hemoglobin in grams from capacity	19	13
Hematocrit	60	45
Plasma volume (c.c. per sq.m.B.S.) (normal 1600)	1,520	1,865
Total blood volume (c.c. per sq.m.B.S.) (normal 2850)	3,800	3,390
Red blood cell volume (c.c. per sq.m.B.S.) (normal 1250)	2,280	1,525
Vital capacity	5.2 L. (normal)	3.4 L.
Maximum breathing capacity	150 L. plus (per minute)	148 L.
Circulation time	16 sec.	

*Case 2, R. G.—The hemoglobin, hematocrit, and red blood cell volume have returned to normal.

and scar. A portion of the parietal pleura had to be excised with the specimen. In the lower anterior portion of the right lower lobe, there was a soft, compressible (Fig. 4) pulsating mass not well delimited but roughly 5 cm. in diameter which transmitted a "thrill" when grasped in the hand. The inferior pulmonary artery was 1 cm. in diameter and when ligated and severed the tumor pulsations stopped, but the mass remained. A short, wide, 2 by 2 cm., thin-walled, pulmonary vein ran transversely from the mass toward the left atrium.

A dissection type of right lower lobectomy was done and the chest wall closed after 100,000 units of penicillin in saline solution were placed in the cavity and the intercostal nerves injected with eucupine. Underwater drainage was used. The patient received 1,800 c.c. intravenous fluids (1,000 c.c. whole blood) during the operation.

At the end of the operation the anesthetist, noted that the patient's cyanosis had disappeared. The postoperative course was fairly smooth, complicated only by a thrombophlebitis of the left lower leg vein used for intravenous fluids during operation. He was out of bed on the fifth postoperative day.

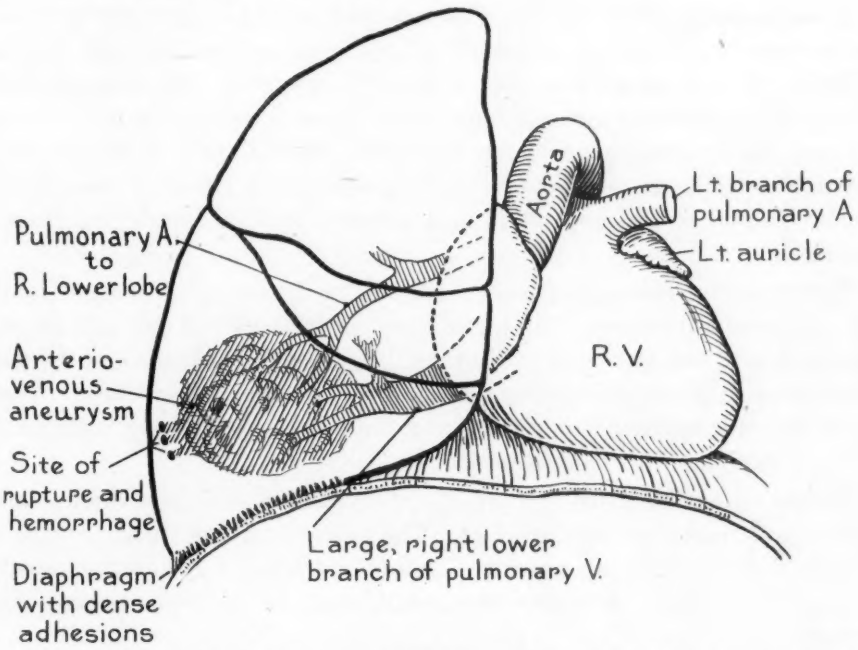

Fig. 4.—Case 2. R. G. Sketch showing the relationship and relative size and position of the arteriovenous aneurysm.

The specimen was examined and reported as consisting of the lower lobe of the right lung, measuring 17 by 11 by 3 cm. Its surface was pinkish gray, mottled with some dark gray areas. The consistency was crepitant throughout. On the lateral surface in the midportion of the specimen was a suture which when removed showed a venous opening which measured 1 cm. in diameter. This was composed of three separate vessels, lined grossly by intima. The lower branch of the right pulmonary artery entered the lung medially. When opened, it was shown to divide into three minor branches, the middle branch of which ran laterally into a multilobulated sinus which measured approximately 3 cm. in diameter. The lower right pulmonary vein emerged inferior and slightly posterior to the bronchus. Two branches emerged from the arteriovenous aneurysm which lay for the most part in the lateral portion of the lung. The aneurysm was ovoid in shape, its long axis being transverse to that of the right lower lobe. Serial section through the remainder of the lung did not reveal any further abnormality. Microscopic findings were reported as consistent with gross findings of arteriovenous aneurysm.

DISCUSSION

Although pulmonary arteriovenous aneurysm is apparently a congenital lesion, typical diagnostic symptoms may not appear until the patient reaches the age of 14 years (Makler and Zion),[9] or 16 years (Hepburn and Dauphinee)[5]; in one of our patients who had reached the age of 27 years the lesion was causing no symptoms and was discovered only by chance radiography. Alexander's[2] patient reached the age of 35 before he developed a persistent cough, his first symptom.

The diagnosis is suggested by a syndrome characterized by cyanosis, clubbing of the fingers and toes, secondary polycythemia, and symptoms of anoxemia, usually in a young patient with an obscure lung tumor and a normal heart. A bruit may be heard over the tumor.

It seems certain that trauma does not play an important role in pulmonary arteriovenous aneurysm, as a history of injury is reported in only one case in this series. One must assume that a gradual, expansive enlargement and thinning out of the walls of the vascular tumor takes place slowly over a period of years and that spontaneous hemorrhage occurs, as in Case 2 of this report, when some slight overexertion increases the intrapulmonary pressure enough to cause a break. Why this did not result in a massive, fatal, intrapleural hemorrhage is not clear.

Pulmonary arteriovenous aneurysms are congenital and mechanical defects in the relationship between the pulmonary arteries and veins, and as such are not amenable to medical therapy, but can be relieved promptly and dramatically by adequate surgical extirpation of the involved portion of lung. There has been no reported operative mortality, and the postoperative lung function studies indicate a return to normal factors.

Before operation there is marked hyperventilation at rest during moderate exercise, and recovery from exercise. The arterial oxygen unsaturation at rest increases during moderate exercise. After operation the high hematocrit and red blood cell volume decreases to normal, and the arterial oxygen saturation improves.

SUMMARY

1. The term "pulmonary arteriovenous aneurysm" seems desirable for this group of cases.

2. Two cases are reported with preoperative and postoperative data.

3. Surgical treatment is urged for every case in which the diagnosis has been established.

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PERIPHERAL ARTERIOGRAPHY

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ARTERIOGRAPHY is the roentgenographic visualization of arterial channels by radiopaque media. I have employed this procedure extensively, using 35 per cent diodrast exclusively for peripheral arteriography. This is in contradistinction to visualization of the great vessels, such as the aorta and pulmonary arteries, which requires an entirely different technique.[6, 12, 32] Practically all the arteriograms were done in cases of arteriovenous aneurysms except in certain diagnostic problems. The problems encountered were as follows:

(1) Determination of arteriovenous communications and the presence of sacs (Figs. 1, 2, 3, 4, 6, 7, and 8)
(2) Abscess versus aneurysm
(3) Question of patency of peripheral arteries after injury (Fig. 9)
(4) Determination of complete thrombosis of aneurysmal sacs
(5) Determination of the exact communication of vascular masses to the parent artery (Fig. 10)

Historical.—Haschek and Lindenthal[1] in 1896 reported the roentgenologic visualization of the arteries of an amputated hand and forearm following the intra-arterial injection of a radiopaque substance about eleven weeks after Roentgen discovered the rays. Trendelenburg in 1902 was one of the first to describe an opaque substance within the blood. His patient had been shot in the heart, and on x-ray, the shot could be seen moving to and fro. The first experiments with a liquid medium were done in 1910 by Franck and Alwens[15] on dogs and rabbits. They used a suspension of bismuth in oil introduced into the heart directly or via the large veins. They then followed the course of these droplets. The earliest good vasograms of the living person were published in 1923 by Berberich and Hirsch.[15] They used a 10 to 20 per cent solution of strontium bromide and their pictures were fairly clear. Brooks[7] in 1924 used a solution of 100 Gm. of sodium iodide crystals in 100 c.c. of distilled water which had been autoclaved. The solution was injected by direct exposure of the femoral artery at the proximal end of Hunter's canal. Nitrous oxide gas was used during the injection because of severe pain. He reported three cases with arteriograms, and felt that this method was of great value in determining the necessity of amputation in instances of peripheral gangrene, and in determining the site of amputation. He also reported that it could rule out the possibility of arterial obstruction. Singleton[40] modified Brooks' method by using spinal anesthesia and did not expose the artery. He used the method in six cases. Three were cases of aneurysms and no difficulty was encountered. The

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other three were cases of gangrene of the feet, and he felt that in two cases the gangrene spread rapidly as a result of using sodium iodide, necessitating a high amputation in one. Death followed in the other. In 1929, Charbonnel and Massé[9] favored the use of sodium iodide as a contrast media but mentioned its irritating effects. Edwards[15] felt that there are many disadvantages to sodium iodide.

In 1923 lipiodol was tried by Sicard and Forestier[39] in dogs without harm; and in 1927 by Carnett and Greenbaum.[8] They used 6 c.c. of iodized oil in the femoral artery of man without harmful effect. They exposed the common femoral artery and passed a tape around it under local anesthesia. They showed excellent arteriograms of the digital vessels, but they were not very

Fig. 1.—This arteriogram demonstrates the simplest type of arteriovenous aneurysm, with the diodrast going just to the site of the fistula in the superficial femoral artery, with no sac. A foreign body is seen at this level. This was confirmed at operation, at which time excision of the aneurysm was done.

clear more proximally. It appears to be dangerous, since it could cause fat embolism, and visualization of large areas is difficult unless dangerously large amounts are used. In 1930 Saito and associates[35] attempted to remove these disadvantages by emulsifying the lipiodol. They used as high as 20 c.c. of this emulsion, injecting the carotid, femoral, and brachial arteries, and obtained excellent arteriograms.

Roesler[34] stated, "A contrast substance injected into the vascular system for the purpose of visualization should fulfill the following requirements: It should contain the greatest possible number of atoms of a heavy element to give sufficient contrast even in dilution. It should be water soluble and have,

preferably, a viscosity similar to blood. It should not decompose in the body and should not precipitate with the blood or other constituents of the body. It should not cause local vascular wall damage or spasm or remote, local, general, immediate, or delayed toxic effects. Elimination should be complete and within a relatively short time. It should not be painful when injected and when a paravascular injection occurs, no severe inflammation should result."

Fig. 2.—This arteriogram visualizes in an excellent manner the common femoral, superficial femoral, and profunda arteries with some venous channels. The arteriovenous communication with the sac and nearby foreign body are well visualized. The dense appearing (light) area in the middle of the thigh represents the true size of the aneurysm which was filled with laminated clot and displaced the superficial femoral artery medially, as was found at operation. Distally may be seen the dilated superficial femoral vein and the constricted superficial femoral artery. Some of the venous system is visualized as well.

Of all the substances used thorotrast would be ideal but for possible late effects due to radioactivity. It is the molecular weight, and not the iodine content of the contrast medium, that influences the degree of radiopacity. Thorotrast is favored by Allen and Camp.[1-4] It is used in 25 per cent aqueous solution of thorium dioxide with the addition of a colloidal solution. Erickson and Rigler[16] have made an extensive study of the possibility of harmful radioactivity of thorium dioxide sol and consider dangerous a much larger amount than that used by Allen and Camp,[1] who used 5 to 12 c.c. in the upper extremity. Radt[29] introduced thorotrast for the delineation of the liver and spleen in 1930. It can be injected into a vessel without pain or deleterious local effect. He later reported observations on animals and human beings, respectively, three and one-half and two years after injection of thorium dioxide sol; harmful effects were not noted. He expressed the belief that the possibility of harmful effects is largely negligible, providing correct amounts are used, and contraindications

to the use of thorium dioxide sol are observed. It was first reported used as an arteriographic medium in 1932 by Moniz and associates,[27] who obtained good visualization of the carotid distribution in the head. Dos Santos and coworkers[12] reported on its use in vasography in over forty patients without untoward effect and obtained excellent pictures of the vessels. No one seems to know the ultimate effect of thorotrast. Altogether it is felt that the use of such a drug is undesirable when more suitable and less toxic drugs are available.

Fig. 3.—This arteriogram accurately visualizes the anatomic findings in an arteriovenous aneurysm with a sac on the arterial side. The aneurysm is in the mid-portion of the superficial femoral artery and vein. The contrast media is seen to visualize the femoral vein as far as the first competent valve and this accounts for the continued good size of the artery distally. These interpretations were confirmed at operation.

Skiodan was used by Edwards,[15] Schuller,[36] Frey and Zwerg,[17] and Pearse and Warren.[28] The fact that this drug is used almost exclusively for intravenous urography attests to its safety regarding general toxicity. However, it has been my experience that there is considerable pain on the intravascular injection of skiodan. Heathcote and Gardner[20] and Pearse and Warren[28] have demonstrated experimentally that there is no intimal damage on injection of high concentration (50 per cent) of the drug. Pearse and Warren[28] also found this to be true in five of their patients where amputation had previously been decided on and was done. In these, the arteries showed no fresh thrombosis or any other evidence of intraarterial damage. Edwards[15] used skiodan preoperatively in varicosities and then examined the tissue removed at operation and found no change.

Diodrast is one of the newer drugs that has been used extensively for urography and has been given considerable clinical trial in phlebography[24] and arteriography. That its use is attended by danger is attested by the report of Pendergrass and associates,[29] who surveyed the deaths and unfavorable sequelae following the administration of contrast media by sending out questionnaires. They found that twenty-six deaths had occurred in addition to those already reported in the literature. The deaths fell into two groups: (1) immediate death due to hypersensitivity or idiosyncrasy to the drug injected, or to colloidal shock, and (2) delayed death. All of the immediate deaths were due to diodrast, but the patients had not received any tests for sensitivity, and in

Fig. 4.—This demonstrates a huge bilocular aneurysmal sac with an excellently patent artery below the sac only accountable on the basis of an occluded distal venous channel.

only a few had a history of allergy been sought. Nine were done with 35 per cent diodrast for intravenous urography, and one (70 per cent diodrast in which two injections of 50 c.c. each were given) for arterial visualization. Twelve cases were found in the literature and most cases showed immediate cyanosis and cardiovascular collapse with gradually diminishing respirations. Autopsy proved pulmonary edema to be a prominent finding. There were sixteen cases of delayed death presumably due to pre-existing major renal damage. Leake[29] stated, "Diodrast is the sort of compound that may combine with amino acids in the body giving rise to various polypeptids to which sensitivity may arise, with resulting allergic symptoms in almost any part of the body." He thought that it should be used with caution where there is any indication of allergic tendency.

Technique of Arteriography.—The technique of arteriography involves the transcutaneous injection of a radiopaque media into an artery and making x-ray exposures at proper intervals to delineate the desired area. Certain precautions are imperative. This is attested by the results reported by Pendergrass and associates,[29] which have been mentioned previously. They conducted a survey of deaths following the administration of organic iodine compounds as contrast media in 661,800 examinations, mostly urographic, and collected in addition to the eleven previously reported cases, twenty-six, representing an incidence of 0.0039 per cent. Certain facts are well evident from perusal of the literature and actual experience. It is important to elicit a history of allergy, to determine the specific gravity of the urine, and to take certain precautions. Diodrast was used exclusively in this series of arteriograms without a serious reaction, as well as in a series of phlebograms to which I referred previously.[24] A preliminary survey of history of allergy was made, and any patient with such a history was carefully observed for sensitivity to diodrast. A high specific gravity of the urine was used as a gross indication of fairly active renal function; but if this was low or fixed, more careful investigation of renal function was made. A preliminary conjunctival test was employed. This ocular test for sensitivity to diodrast was done, as recommended by Harris and Archer[19] for use prior to intravenous urography. They feel that this is better than the subcutaneous, oral, and preliminary small intravenous tests. They used one drop and examined the conjunctiva one and one-half to three minutes later. There are three general types of reactions:

1. Minimal injection of the conjunctiva—usually the subject will experience a hot flash and some nausea.

2. Moderate injection of conjunctiva and scleral vessels—usually the subject will experience nausea, emesis, vasomotor dilatation; occasionally generalized pruritis, urticaria, and some slight swelling of the upper respiratory membranes. These are usually temporary reactions and respond readily to the administration of adrenalin.

3. Marked injection of sclerae and conjunctiva—this is an absolute contraindication.

If this test was negative, 1 cm. of diodrast was injected intra-arterially, and if there was no reaction within one minute, the procedure was completed. One cm. of adrenalin, ready in a syringe, was always made available before the procedure was started. That this is important is stressed by the report that Pendergrass and associates[29] were able to collect, in which it was felt that the prompt administration of epinephrine saved the patient's life after a reaction in which the hypersensitivity simulated anaphylactic shock. It is important to palpate the peripheral arteries after arteriography to ascertain any spasm and to treat it immediately.

Upper Extremity Arteriography.—A few centimeters of 0.5 per cent procaine hydrochloride are injected over the distal portion of the brachial artery into the skin and subcutaneous tissues. A sphygmomanometer cuff is placed around the arm near the shoulder. The position of the whole upper extremity is abduction and supination. If it is a question of the forearm region alone,

pronation or a lateral position may be chosen. A posteroanterior projection is used for the visualization of the vessels of the hand. Fifteen cubic centimeters of diodrast are then placed in a syringe, and a 19 gauge needle is used to make the arterial puncture. As soon as arterial blood from the brachial artery pulses into the barrel of the syringe, the cuff is rapidly inflated above the systolic blood pressure, and the radiopaque material is injected. The needle is withdrawn quickly and the first roentgenogram made. The cuff is then deflated quickly to the level of the diastolic blood pressure for a period of several pulse beats, to permit the injected material to be carried farther distally. Then the cuff is reinflated quickly to its previous pressure, and the second roentgenogram is made. The x-ray tube is centered over the expected site of the lesion.

Lower Extremity Arteriography.—It is possible to visualize practically any portion of the arterial system of the lower extremity by injection of contrast media into the common femoral artery, and adjusting the x-ray tube and Bucky diaphragm to the site to be visualized, and delaying the exposure an adequate period. This method is achieved only after a period of trial. It is important to take a preliminary exposure of the area that is to be visualized so that the proper x-ray factors will be employed during the injection of the contrast media.

The exposure is best made with the patient in an anteroposterior position. A 14 by 17 film is used. The skin in the femoral region is prepared by shaving and is then sterilized with merthiolate. One-half per cent procaine is injected intracutaneously and subcutaneously over the common femoral artery. The artery is palpated and located just distal to the inguinal ligament. Thirty cubic centimeters of 35 per cent diodrast is then put into a syringe, and using a 19 gauge needle, which is inserted distalward, the artery is located. The needle is felt to rest on the artery and can be seen to move with each pulsation. It is then firmly held against the artery and will "insert itself" into the artery after which bright red blood will spurt into the syringe. The needle is then advanced 1 to 2 cm. in the lumen of the artery so that no leakage or disengagement will occur during forceful injection. This injection is done with one hand while the artery is compressed proximally during injection with the other hand. At the end of rapid injection, and while still compressing the artery proximally, an x-ray exposure is made and then another 14 by 17 film inserted, after which x-ray exposure is repeated following removal of manual compression of the artery. The exposure is delayed according to the distance the dye must travel for proper visualization, and by this method the entire major vascular system of the lower extremity, including the plantar artery, can be visualized. The profunda femoris artery ordinarily will not be visualized, unless some obstruction of the superficial femoral artery is present. Only representative arteriograms are reported in this publication, although it is to be emphasized that many more were done.

Arteriography in Aneurysm.—Arteriography was employed extensively to visualize aneurysms and to delineate aneurysmal sacs (see Figs. 1, 2, 3, 4, 6, 7, 8, and 10). Technically, it is important to emphasize that, in performing

arteriography in the presence of arteriovenous aneurysms, it is extremely easy to enter the vein rather than the artery because it will be dilated and thickened and will contain bright red blood. This was done in one case (see Fig. 5) and merely outlined the femoral vein. Allen and Camp[1] showed an arteriogram of a popliteal aneurysm with sac and an arteriovenous fistula in the region of the middle phalanx of the index finger. Bird[5] reported arteriography in an arteriovenous brachial aneurysm, injecting 10 c.c. of diodrast in the vein in the cubital fossa and compressing the artery proximal to the fistula. He also showed arteriograms before and after excision of a plantar aneurysm. These were made by injecting 10 c.c. diodrast directly into the exposed posterior tibial artery.

Fig. 5.

Fig. 6.

Fig. 5.—This demonstrates an easily made error in arteriography of arteriovenous aneurysm. The vein becomes not only dilated but thickened and transmits an active pulsation if a large arteriovenous fistula is near the common femoral vein. In such instances the contrast media can be easily injected into the vein with the mistaken idea that it is the artery, as red blood under pressure will return through the needle. In this case the common femoral vein and its tributaries are well visualized.

Fig. 6.—This arteriogram demonstrates the huge dilatation of the venous portion of the involved arteries and veins. It is noted that even the parafemoral collateral venous channels, so important in venous occlusion, are hugely dilated. The aneurysm proved to be at the site of the arrow and was a simple arteriovenous communication.

Dos Santos, Lamas, and Caldas[13] listed six items to be determined by the use of arteriography in aneurysm: (1) the variety of aneurysm, (2) its relations, (3) the permeability of the sac, (4) the state of the collateral circulation, (5) the exact relation of the arteries and veins in arteriovenous aneurysms, and (6) the postoperative result. Horton,[21] using 25 c.c. thorotrast by injecting the femoral artery and compressing the artery proximally, claimed to have been

the first to use arteriography to identify an arteriovenous fistula of the femoral artery, which was the only accurate means of localizing the fistula except operation. Horton and Ghormley [22] reported two cases of congenital arteriovenous fistulas visualized by arteriography and felt that these were the first two in the literature. Arteriography overcomes the previous difficulty of locating the abnormal communications. These were in the finger and hand and were treated by surgical means. It is noteworthy that Lewis[22] found only thirty cases of congenital arteriovenous fistulas of an extremity recorded in the literature in 1930. In nineteen, surgical exploration was attempted in an effort to locate the fistula, and this was followed by amputation of the involved extremity in eleven cases

Fig. 7.

Fig. 8.

Fig. 7.—This demonstrates a simple arteriovenous aneurysm of the posterior tibial vessels with prompt return of the dye. This case also proved to have an arterial aneurysm of the peroneal artery which was not visualized by arteriography and emphasizes that all findings at arteriography are not conclusive.

Fig. 8.—This arteriogram demonstrates that even the plantar vessels can be visualized by this technique. This case proved to be an aneurysm of the lateral plantar artery and vein, and this was excised.

(58 per cent). Veal and McCord[42] reported the use of arteriography (and the oxygen saturation test) in the diagnosis of congenital abnormal arteriovenous anastomosis of the extremities. They felt that this procedure is of great value. Yater and White[46] reported a case of arteriovenous aneurysm with sac just below the bifurcation of the brachial artery and showed an arteriogram done with thorotrast. Yater and Otell[45] felt that there were few contraindications to the use of thorotrast in quantities used for arteriography. Yater[44] reported four cases of aneurysm visualized by thorotrast and felt that this was of great help in acquired arteriovenous fistula.

Early Diagnosis of Bone Malignancy.—Arteriography as an additional aid in the diagnosis of malignant bone lesions was first presented by dos Santos, Lamas, and Caldas.[12] Experience has convinced Inclan[23] that arteriography can be of definite assistance in the early diagnosis of malignant lesions of bone, provided that the lesion is localized so that the early circulatory changes are evident by x-ray examination. Shallow, Baker, and Fry[38] felt arteriography to be superior to diagnostic biopsy in the diagnosis of malignant bone lesions since there is danger of spreading a malignant bone tumor by diagnostic biopsy. They agreed with Inclan. Inclan[23] used thorotrast in doses of 10 to 20 c.c. He described the findings in these lesions: (1) filling in of the stroma of the new

Fig. 9.—This represents an arteriogram to determine patency of the popliteal artery and more peripheral channels in a case where further operative procedure about the knee was contemplated, and it was felt that no procedure was desirable if essential collaterals would be destroyed, resulting in loss of limb. A nerve suture was eventually done.

growth by numerous vessels, forming a bizarre network and showing extension of the invading tumor; (2) the presence of new atypical arterial circulation, with pedicles from the main artery and numerous irregular branches entering the bone lesion, thus, clearly defining the limits of the lesion; (3) the premature appearance of a very rich venous circulation, with formation of gross venous pedicles arising from the tumor and entering the neighboring vein; and (4) an increased arterial circulation appearing distributed perpendicularly to the bone.

Necessity and Level of Amputation.—Brooks[7] presented two cases to confirm his impression that arteriography has been of great value in determining

the necessity of amputation in instances of peripheral gangrene, and, in those instances in which amputation was indicated, in determining the site at which amputation should be done. Pearse and Warren[28] reported two cases in which amputation was not done because the arteriogram showed patent vessels. Schuller[36] reported a case in which arteriography was very helpful in deciding the site of amputation in a case of arteriosclerotic gangrene, where clinical tests showed vascular insufficiency up to the knee, and no peripheral pulses could be felt, yet the arteriogram showed a patent peroneal artery.

Fig. 10.—This arteriogram visualizes a cirsoid aneurysm of the superior medial geniculate artery, and on the original film demonstrated the communication with the parent superficial femoral artery.

Question of Patency of Peripheral Arteries After Injury.—Not infrequently the question arises as to the necessity of determining the patency of a peripheral artery following injury. It is desirable to determine this where so-called "critical arteries" are involved. In the extremities, one of major considerations is the popliteal artery. In one such instance (see Fig. 9), there had been marked damage to the structures in the popliteal region from previous fracture. Further major operative procedure was contemplated regarding neurorrhaphy, and it was clinically impossible to determine popliteal arterial patency. This was

solved by arteriography, which demonstrated a satisfactory major arterial channel and thus encouraged major surgery in the popliteal space without fear of the loss of the extremity.

Differential Diagnosis.—Arteriography has been used to locate the site of embolism,[26] to detect the presence of arteriosclerosis,[1] to determine collateral circulation, to detect arterial spasm,[1] to detect a torn artery in fracture,[5] and to aid in the diagnosis of thromboangiitis obliterans.[1-3, 8, 35] I found arteriography of value in one case in which a differential diagnosis between abscess and aneurysm could not be made. Arteriography was done, since no murmur could be heard in a swollen leg, and aspiration was not conclusive. This demonstrated an aneurysmal sac at the end of a torn posterior tibial artery in a hugely swollen leg. This was removed with a satisfactory result. That an error can be made in diagnosing abscess for aneurysm is demonstrated by reports in the literature.[18]

Determination of Complete Thrombosis of Aneurysmal Sacs.—It is well known that certain aneurysms will obliterate spontaneously. This is determined easily in cases of simple arteriovenous fistulas by clinical means but becomes difficult or impossible in arterial aneurysms. As clotting occurs in a saccular arterial aneurysm, it becomes increasingly difficult to determine complete obliteration. This can be easily determined by arteriography, and I have used it for this purpose with satisfactory results.

Determination of Exact Communication of Vascular Masses to the Parent Artery.—This is well demonstrated by a case of cirsoid aneurysm of the medial geniculate vessel, secondary to a contusion. Arteriogram (see Fig. 10 accurately outlined the communication and aided in the diagnosis and proper treatment.

Complications.—No complications were noted in this series, except in one case where the resulting spasm with severe pain required morphine, when injecting diodrast in an artery in an individual with arteriosclerosis. This resulted in diminished peripheral arterial pulsation. That this can be a serious complication is noted in a report by Wagner,[43] in which arteriography in the upper extremity in a child, aged 14 months, resulted in marked ulceration following persistent absence of the radial pulse, which must have resulted from thrombosis.

Complications following arteriography are most prone to occur at the two extremes of life, because in infancy and childhood the vessels are particularly susceptible to spasm, those of the upper extremity more so than the lower, and because in old age the incidence of arteriosclerotic occlusion is increased and the collateral circulation becomes progressively worse. Trauma to the artery as a result of puncture by the needle, and the force of injection by arterial distention, may in themselves provoke reflex vasoconstriction. The reactions may be local or systemic. The local reactions consist of hematomas, extravasations, and thrombosis. The more remote effects are severe vasospastic reactions, hematemesis, anemia, flushing of skin, erythematous eruptions, nausea, vomiting, cyanosis, respiratory distress and fall in blood pressure, death from allergy, and hypersensitivity.

A hematoma may occur at the site of arterial puncture, but this is usually easily prevented by aspiraton on withdrawal of the needle and then firm digital

pressure for one minute. It usually absorbs spontaneously. No such incident occurred in this series. Demel[10] stated that, in arteriosclerosis, in one out of 300 cases there may be bleeding from the artery, readily controlled by a suture through the adventitia. Dos Santos and associates,[13] among 1,500 arterial punctures, had only one case of persistent bleeding, necessitating ligation of an atheromatous femoral artery, and the patient recovered without gangrene of the extremity. Extravasation of the contrast media should rarely occur. Displacement of the needle can occur, however, and in 411 arteriographies, with the use of thorotrast, dos Santos[14] had only eight extravasations. Dimtza and Jaegar,[11] among seventy transcutaneous arterial injections, had six extravasations, but they were not followed by serious consequences except nausea and fever. Absorption and resolution of the resultant inflammatory process is slow. Diodrast will usually absorb, but thorotrast may diffuse by way of the lymphatics and slowly form a mass some distance from the original site of injection. Dos Santos[14] reported the development of suppurative mass in the iliac fossa two years after femoral arteriography with thorotrast, complicated by extravasation of the contrast media.

Among the serious complications are severe immediate vasospastic reactions in the injected limb. In almost all instances these have followed the use of organic iodine compounds rather than thorotrast. Dos Santos,[14] in 129 arteriographies with organic iodine compounds, had six cases in which gangrene was aggravated, in contrast to no vasomotor reaction in more than 300 with thorotrast. The vasomotor reaction is manifested first by severe pain in the limb and blanching, followed by venous stasis. Later scattered violet plaques may occur. Motor paralysis may occur, skin and tendon reflexes may be abolished, and anesthesia may be present, distal to the zone of injection. The pain usually subsides in two or three days. The cyanotic plaques slowly resorb, passing through the colors of a hematoma, and blisters may occur. Movement and sensitivity gradually return and in a week to ten days the limb may become normal. In other cases a pre-existing gangrene may be aggravated.

In a few instances the puncture site has been surgically explored. The muscles are engorged with dark blood which flows readily from the veins, but does not spurt from the arteries. On exposing the area of the puncture, there is no hematoma, and the puncture site is not identifiable. According to Leveuf[25] the artery does not pulsate, and aspiration with a needle fails to obtain blood. On opening the artery a soft clot is formed which does not prevent passage of the needle into the lumen of the vessel. The arterial lumen often contains a recent thrombus undergoing organization.[25, 37]

CONCLUSION

Peripheral arteriography is a valuable adjunct to the diagnosis and treatment of arterial lesions. The following indications are recognized by the author:

(1) Visualization of aneurysms and fistulas and delineation of aneurysmal sacs
(2) Early diagnosis of bone malignancy

(3) Location of the site of an arterial embolus
(4) Determination of collateral circulation
(5) Outlining of arterial injuries and determination of patency following injury
(6) Differential diagnosis of abscess and aneurysm
(7) Determination of thrombosis of saccular arterial aneurysms
(8) Determination of communications to vascular masses of the parent vessel

It is recognized that there are certain dangers to arteriography, but careful adherence to detail will avoid complication. It is felt that the procedure is a valuable one and deserves much consideration. Despite often repeated statements that such a procedure is unnecessary because clinical diagnostic methods are adequate, it is felt that such individuals are overlooking an easily performed and valuable adjunct to diagnosis and treatment.

Acknowledgment.—The patient reported in Fig. 10 was operated upon by Dr. W. E. Rector, and the author wishes to acknowledge his help in securing several of the arteriograms reported.

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CHRONIC EVENTRATIONS AND LARGE HERNIAS

Preoperative Treatment by Progressive Pneumoperitoneum—Original Procedure

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DURING May, 1940, an obese woman, aged 65 years, suffering from heart disease, was admitted as an emergency case because of large incarcerated supra-umbilical eventration, without obstruction. The patient was in poor general health. Under careful observation she was given two small intraperitoneal injections of oxygen, and after one week the incarceration disappeared. A fortnight later, following repeated insufflations of oxygen, she was operated upon under local anesthesia, and both the operation and the imbricated aponeurotic closure were performed without difficulty. The postoperative course was uneventful.

At the Twelfth Argentine Surgical Congress (October, 1940), in a paper on "Postoperative Eventration" presented by Professor J. M. Jorge and me, the following statement occurred:

"Although our present experience only allows us to bring a preliminary report to this Congress, one of us (Goñi Moreno) has attempted the preoperative preparation of cases with chronic postoperative eventration or gigantic hernias, with a method which we have not found previously recorded. It consists of a *progressive pneumoperitoneum* with injections of oxygen . . ."

This was apparently the first time that a pneumoperitoneum had been used for therapeutic purposes in eventrations and hernias. It had been used previously only in the treatment of certain forms of bowel and peritoneal tuberculosis, and both in radiographic and laparoscopic diagnosis.

Since 1940 my assistants and I, or other Argentine and South American surgeons, have operated upon approximately fifty patients of both sexes with large neutral hernias, usually uncomplicated, who had been prepared by this procedure. No accidents occurred and the procedure has the advantage of being simple and efficient.

Professor Manuel Riveros, of Paraguay, has informed me that he already has five successful cases to his credit, and is very enthusiastic about this method.

I understand that it is being used satisfactorily in various surgical departments in Argentina, Uruguay, and Chile.

Few publications have dealt with the method. In 1944, two senior physicians in my department brought this subject up to date in a communication read at a meeting of the Argentine Society of Surgeons.† The same year a

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†Russo, A. G., and Mazzini, E. J. B.: El neumoperitoneo preoperatorio en la cirugia de las grandes hernias y eventraciones, Bol. y trab., Soc. argent. de circujanos 5: 1071-1085, 1944.

report was made* on the successful use of the method in the case of an elderly woman who was addmitted in severe shock and suffering from a strangulated postoperative hernia.

Progressive pneumoperitoneum has occasionally been used in chronic complicated eventrations, and in those cases only to obviate an emergency, but its real indication is in uncomplicated cases, as a means of preoperative preparation.

Rationale of the Procedure.—Two questions arise concerning the mechanism by which repeated pneumoperitonea are efficacious in large neutral hernias. Is it a substitute for the weight reduction therapy or does it permit an adjustment of respiratory balance?

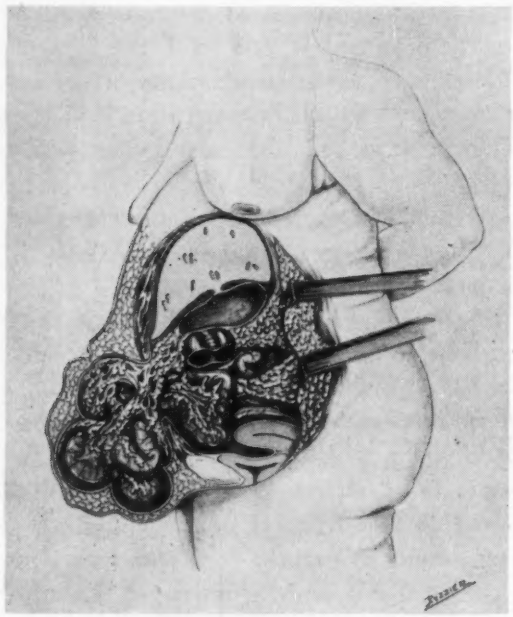

Fig. 1.—Pathologic state in a chronic eventration.

In the first place, it acts upon the disproportion between the abdominal container and its contents, most of which are lodged in the large sac, graphically described as "the second abdomen." Were the distended viscera, omenta, fatty and edematous mesentery—all of which have lost their "rights of domicile"—suddenly returned to the abdominal cavity, not only would this produce embarrassment by increasing the abdominal contents, but also the closure of the peritoneum and other parietal layers would be difficult, and the sutures would be subjected to excessive tension; hence, the fear of recurrences.

Second, the postoperative condition of the patient would be hindered by the effects of the sudden increase in abdominal tension in a patient whose breathing is already deficient. Obesity, with its tendency to pulmonary complications and phlebothrombosis resulting from chronic venous stasis, increased

*Ottolenghi, E. L.: El neumoperitoneo en la reducción de la eventración post-operatoria estragulada (comunicación previa), Dia méd. **16**: 1149-1150, 1944.

respiration disorders, and the lack of sufficient thoracic respiration, produces a poor postoperative risk.

By prepoperative intraperitoneal air insufflation the postoperative changes, that is, increased intra-abdominal tension, diaphragmatic elevation, and respiratory difficulty, are produced but to a minor degree. For this reason, the first injection should be done cautiously, although the disturbances it produces usually disappear rapidly. The second and third injections are generally well tolerated, and the amount of air and pressure may be increased considerably. A remarkable feature of pneumoperitoneum is that, in spite of the greatly increased intra-abdominal pressure, there is no reduction in the patient's vital capacity, as determined by spirometry.

The patient can be given four to five sessions of *progressive pneumoperitoneum,* over a period of three to four weeks and in quantities that in the last session may reach the extraordinary amounts, as much as 6 to 8 L. and pressures of 30 to 40 mm. on Claude's scale; whereas in the same patient, 500 to 1000 c.c. as initial dose would have produced marked symptoms due to abdominal hypertension, such as dyspnea and pain in the left shoulder, even though the intraperitoneal pressure did not rise above 10 mm. The patient's vital capacity, which before treatment may be 1,500 cm., is likely after the first injection to decrease to 1,000 cm., but later will rise and become stabilized between 1,500 and 2,000 cm. by the end of the treatment.

When the abdomen is opened and all the air expelled, the patient has a feeling of relief, the abdominal walls become flaccid, and the viscera show no tendency to protrude. The operative closure is much easier than when deep anesthesia is used. Moreover, aponeurotic imbrication is easy, and the sutures are not subjected to tension.

I have operated upon some patients under local analgesia, just to prove that this is possible. In a large eventration in an obese woman, I have used 800 c.c. of a ½ per cent solution of percaine. Spinal or general anesthesia are preferable, however.

The dissection of the sac and liberation of adhesions becomes easy, because of the stretching produced by the preoperative air pressure.

Vital capacity improves with the release of the air and breathing becomes freer; the postoperative course is uneventful.

Neither I nor other surgeons who have followed this technique have seen a single pulmonary or venous complication in the large number of large eventrations treated. I have had no complication resulting from insufflation of the peritoneum. The method is harmless and has many advantages, and I would even go as far as to say that it solves all technical and postoperative difficulties.

It is, however, contraindicated: (a) in aged patients in poor health, with diabetis and uremia, etc., unless they are emergency cases in which all other forms of treatment have failed in relieving a strangulation, and even this may fail; (b) in decompensated heart cases; (c) in blocked or strangulated hernias or eventrations which have existed for several hours.

As a *relative* contraindication—which means that one must act *cautiously* —we must consider the chronic eventrations with a narrow ring, that have undergone repeated incarcerations and strangulations. Even in such cases, the pleating of the sac by means of adhesive tape and bandaging will allay any acute hazard. I draw attention to this contingency because of an experience with one such case.

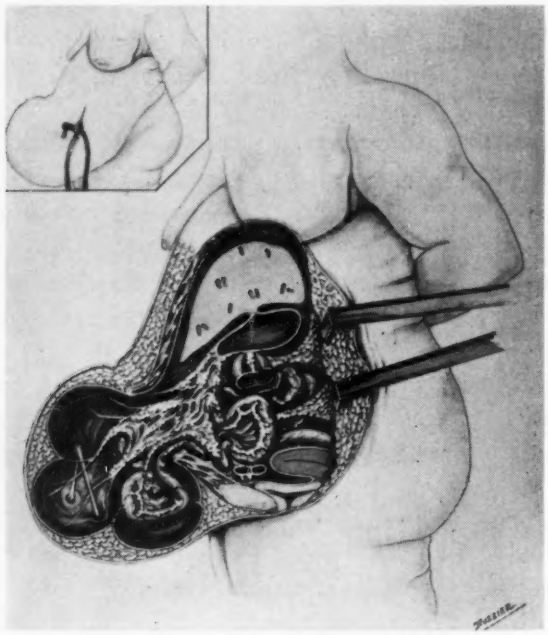

Fig. 2.—During the treatment.

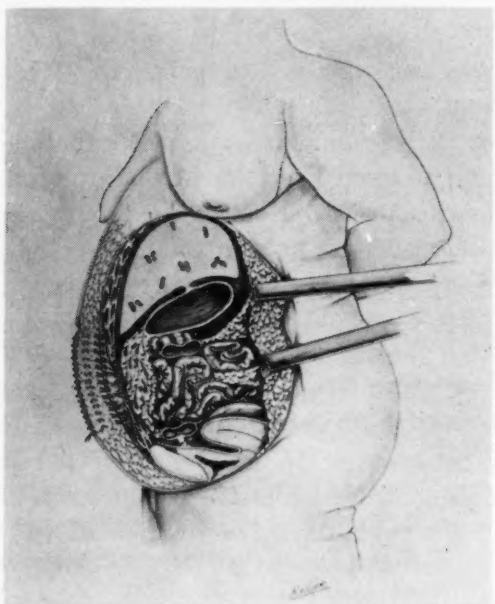

Fig. 3.—After operation, no suture tension can be observed.

Some will suggest that an intensive reduction in weight and well-controlled breathing exercises will prepare the patient satisfactorily for operation.

Even when this is done, it must be recalled that, at times, it is necessary to crush the phrenic nerve in order to increase the abdominal capacity.

It has not been an easy matter to solve the problem. My own earlier experience (prior to using pneumoperitoneum) had convinced me that the treatment based on weight-reduction was insufficient. It will reduce the weight of an obese person weighing 270 pounds by some fifty pounds, which will make little difference in the local conditions; besides, it is a very protracted treatment that is seldom tolerated by the patient because of various reasons, the financial one being one of them.

The treatment I suggest lasts at most from two to three weeks. Although I have always kept the patients in bed, I believe it could be carried out as an ambulatory procedure.

Preparation of the Patient.—The patient should not take any food during several hours prior to the treatment. Although it is not necessary to be too severe in this respect, it is important to perform the pneumoperitoneum some time after food ingestion, because of the digestive disorders that can appear. Once admitted to the ward, the patient should be placed in the Trendelenburg position. Well-controlled breathing exercises should be carried out daily by means of a spirometer and the various readings must be recorded on a chart for future reference.

A careful observation of patients treated by pneumo injections enabled us to establish that a large proportion of the gas entered the "second abdomen," formed by the eventration through the defect in the aponeurosis of the abdominal wall. This escape of the gas into the hernia nullifies the purpose of the pneumoperitoneum (a uniform abdominal pressure) since the tension becomes much higher in this region than in the rest of the abdomen. This difficulty can be solved before beginning the treatment by using a procedure very similar to that applied by pediatricians in the treatment of umbilical hernias in babies. After applying benzoin tincture to protect the skin of the abdomen, the hernia is reduced by invaginating the sac along with a fold of skin and bringing the sides of the opening as near together as possible. While they are held in this position, an assistant applies several strips of wide adhesive tape across the abdomen, the width and position of which bear a direct relation with each individual case and the surgeon's dexterity; the important feature is that they should produce as near as possible the ideal objective—the closure of the hernial sac. In the patients who are not confined to bed, the upper edge of the horizontal strips of adhesive tape may produce ulceration of the skin which can be prevented by not allowing the patient out of bed, even for a short time, without wearing a tight body bandage.

With this simple procedure, we have had no mishaps in over 300 pneumoperitoneum injections in eventrations of all sizes and of the most capricious shapes, and which have been injected with as much as 8 L. of air in one

single session (Case 39624) attaining an intra-abdominal pressure of 32 cm. on the Claude manometer.

Before starting the administration of the pneumoperitoneum, we carry out a careful examination to estimate the patient's general state of health, to establish the operative chances, and to determine whether the pneumoperitoneum may be undertaken without any risks. Also prior to the injection, obese patients should be kept in bed for three or four days in a moderate Trendelenburg position; breathing, lower limb exercises, and massage must be carried out twice daily and a convenient calorigenic diet prescribed.

Moreover, during the three or four days that precede the first session of pneumoperitoneum, the bowels should be emptied by daily enemas.

Technique of Air Injection.—The patient lies on the back, in a moderate Trendelenburg inclination. The strips of adhesive tape are applied or renewed, as the case may be. Spirometry is then determined.

The surgeon, wearing sterilized gloves, applies the antiseptic solution to the skin of the left iliac region of the abdomen. Under procaine anesthesia, a wheal is raised in the middle of a line joining the anterior superior spine with the umbilicus. A spinal puncture needle is introduced into the abdominal wall until it reaches the peritoneal cavity; that this has taken place is confirmed by a special sensation of going through a resistance which has opposed its progression. In the case of a first puncture, or when it is thought that owing to the long time lapsed since the last one there is no remaining gas, a small amount of air should be injected by means of a syringe. If this is done easily, it is almost certain that the point of the needle is within the cavity. Provided it is not the first injection, we systematically connect the needle to the apparatus used to supply the air; the manometer will register the pressure of whatever residual air there is in the abdominal cavity.

Once it is certain that the needle is in the right place and the pressure has been noted, air is slowly injected, its pressure and rate being regulated by means of Richardson's insufflator.

When it is desired to know the amount of air that has been injected (a purely documentary interest, because what is important is the intra-abdominal air pressure and not the number of liters), we use two saline solution bottles, one full of water and the other empty. The air injected by a Richardson's insufflator will alternatively force the water from its container into the other bottle and thus inject an equivalent amount of air into the abdomen. The size of the bottle (500 c.c. in our department) multiplied by the number of times this amount has been injected, will give an idea of the size of the injection. If we also wish to know the pressure, the abdominal cavity can be connected with a manometer by means of a two-way key.

The elimination on one of the bottles saves time, as it avoids both changing the tubes backward and forward from one bottle to the other and the need of an assistant.

From time to time the manometer is connected so as to control the pressure reached and thus estimate when the useful one is obtained—somewhere

in the neighborhood of that of the previous injection (in the event of it being the first injection, it is the highest amount of air tolerated by the patient, without discomfort). The ideal is to be able to inject more, but this is not always possible; *one must not insist in doing so* but must consider the patient's tolerance.

On some occasions, during the first or successive injections, a few difficulties may arise, such as acute pain, like a stab near the puncture zone, which may radiate toward the corresponding hemidiaphragm. This contingency appears suddenly and disappears in the same way if the injection is stopped for a few minutes, after which it may then be resumed successfully.

THE INJECTION OF AIR

So long as their mechanism of production is understood, this dual feature of both sudden onset and disappearance of pain and its short duration is the best sign for differentiating the slight and passing handicaps from those that indicate that the patient's tolerance peak has been reached.

When the aforementioned contingency appears, after a brief pause, the air injection should be continued as slowly as possible, controlling the rate of air passage by means of a Richardson's insufflator.

If, on resuming the injection after the pause, the pain reappears with identical characteristics, a further pause may be tried; however, should the disturbances continue, the session must be postponed until another day.

Should everything go well, the air can be injected at a rate of 1 L. (1¾ pints) per 1½ minutes, and continued until the patient begins to complain of the following disorders: (a) uncomfortable distention, and (b) diffuse pain, that begins at the site of puncture and then affects the whole of the abdomen in a more or less capricious way. It is usually more marked in the right flank, over the pubis, and the left hemidiaphragm; occasionally the pain extends to the left shoulder.

These are the signs that should be recognized and given due consideration by anyone who attempts a pneumoperitoneum and wishes to obtain its full benefits.

In order to decide when a session should end, one of two methods may be followed: eithere the injection of air must be continued until the aforementioned disorders appear, or the useful pressure is determined beforehand according to the results of earlier injections, namely, an equivalent or slightly larger dose.

After registering the pressure, the needle is withdrawn, the puncture covered with cotton-wool dipped in collodion or alcohol, and a body bandage is applied.

After a five minute pause to allow the patient time to quiet down, the breathing is controlled by spirometry, and the session is over.

After the administration of a pneumoperitoneum, patients are given very little food (the appetite is generally low) and on no account are they allowed to get up until the next day.

Later on (between twelve to twenty-four hours) patients may present certain disorders, such as dyspnea, palpitations, headaches, and back pains, all of which will disappear rapidly by returning the bed to horizontal position and by the administration of ¾ to 1½ gr. of phenobarbital.

The technique just described makes it evident that the real guide to the course of this treatment lies in the figures resulting from research done on intraperitoneal pressure.

However, we have not yet been able to apply this criterion as a matter of routine, because of the difficulty in obtaining good tensiometers of late. Notwithstanding, we have decided to follow the criterion based on the pressure record and not on the amount of gas injected, for the following reasons:

1. Because the useful effect is not determined by the number of liters injected, but by the pressure which the gas exerts on the abdominal wall.

2. Because there is no direct relation between the number of liters injected and the intraperitoneal pressure. This assertion is further supported by the fact that it is influenced by many other causes, such as size, elasticity and tone of the abdomen and its walls. It must also be remembered that the injection of 2 L. of air will not have the same effect in the first session as in the fourth or fifth, because in the latter, the abdominal walls have already attained a certain degree of relaxation and their tolerance has increased.

3. Tensiometry also enables us to determine the presence and amounts of residual air, while if the number of liters injected in the previous session were the only source of estimation, it would never be possible to ascertain the new amounts to inject.

Besides being the only useful figure, pressure readings may be obtained with accuracy at any moment, and will thus allow comparative determinations.*

4. *Time that should elapse between successive sessions:* No figures can be given as a fast rule, as the intervals depend on certain individual factors on the part of the patient, such as tolerance, rate of absorption, etc., moreover, there is also the surgeon's criterion to be considered.

If the useful pressure lies in the neighborhood of that reached in the previous session, but it is found that there is a steady decrease through absorption, the only way in which it can be maintained more or less stable is by more frequent injections. This would be the ideal preoperative technique, but in practice there are numerous difficulties and our own experience tells us that the best results are attained with an interval of roughly five days between injections. Although we do not claim to make a fast rule of this five day lapse, both periodical abdominal palpations revealing a certain *relaxation,* and the control of *pressures* have led us to consider it the most appropriate one.

5. *Operative opportunity* is an interesting point, as two sets of factors must be taken into account: the individual patient and the surgeon's criterion,

*These results, estimated by the pressure readings, are the fruit of a careful study carried out by one of my assistants, Dr. Juan C. Aguilar.

namely, the time when he considers that, from the abdominal and respiratory point of view, the patient is most fit to undergo the operation.

After one has acquired a certain experience in pneumoperitoneum technique, both a comparison between the abdominal distention when pressure reaches its peak, as compared with that before injection, and the flaccidity of the abdominal walls in this condition, if correctly interpreted, will provide very important data for making this decision.

The moment vital capacity becomes stabilized or rises slightly after four or five sessions and the patient realizes that he breathes more freely, it can be considered that the preparatory period is about finished.

Earlier in our experience, occasionally patients complained of pain during the air insufflation which was due to the gas being injected at excessive pressure and rate, producing a "surprise reflex" much stronger than normal, and giving rise to a painful contraction making it impossible to continue with the injection. As we now inject the air very slowly (1 L. per 1½ minutes), we have never had to suspend the treatment.

The treatment usually lasts two to three weeks, in which the patient receives five to six injections (one every five days). Besides using pressure control and the number of liters injected as a physical index, we take progressive spirometry as a physiologic index of vital capacity. Although this last index does not always follow a parallel course to the progress of treatment, it must be admitted that, owing to a purely mechanical factor, there is a drop in the vital capacity of a patient subjected to a high intra-abdominal tension. However, if daily spirometric readings taken during the breathing exercises do not show a reduction, it is because the treatment is following a very good course. This index will be all the more valuable for establishing an improvement in pulmonary ventilation, when vital capacity increases by 500 to 1,000 c.c. before removing the intraperitoneal air because it would mean that, once the obstacle to free diaphragmatic excursion has been removed, spirometry will register a marked increase in vital capacity.

CUSHING'S SYNDROME ASSOCIATED WITH FUCHSINOPHILIC STAINING REACTION IN THE ADRENAL

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MOST of the standard textbooks of medicine and pathology describe Cushing's syndrome as one in which there are painful obesity of the face, neck, and trunk, early amenorrhea in females and ultimate sexual impotence in males, hypertrichosis of the face and trunk in females and preadolescent males, loss of hair of the scalp, dark red striae of the skin especially on the abdomen, hypertension, diminished sugar tolerance often with hyperglycemia and glycosuria, osteoporosis with pain in the bones, and general bodily weakness.

Some of the pathologic findings associated with Cushing's syndrome or the adrenogenital syndrome reported are: adenomas and carcinomas of the adrenal cortex, hyperplasia of the adrenal cortex, fuchsinophilic granules of the cells of the adrenal cortex, basophilic adenoma of the anterior lobe of the pituitary, arrhenblastoma of the ovaries, granulosa-cell tumors of the ovary, tumors of the pineal body, and tumors of the thymus.

The case is presented because of its surgical interest and the hyperplasia of the androgenic zone noted in the adrenal, made manifest by the fuchsinophilic staining reaction. No other pathology could be demonstrated, by x-ray or exploratory laparotomy, to account for the Cushing's syndrome. Oppenheimer and Silver reported the finding of these fuchsinophilic granules in virilism, but also in adenomas of the adrenals, found incidentally at post mortem. Cahill and his co-workers reported finding these granules in the adrenals of dogs and in human beings without virilism; however, the granules were more marked in adrenal-cortical tumors with virilism. Sudds has demonstrated these granules in 24 per cent of adult males and in 28 per cent of adult females. Several controls were examined in this case—ranging from the newborn infants dying of atelectasis of the lungs to patients in the older age groups dying of coronary thrombosis, and in no instance did the fuchsinophilic staining reaction approach that of the adrenal in Cushing's syndrome. In the newborn infant, the fuchinophilic granules were almost completely absent; in the older age groups, they were more of a "spotty" type. Vines, by examining some sixty fetuses, demonstrated this androgenic zone or fuchsinophilic staining reaction in the adrenal. In the male fetus, it was present between the ninth and twentieth weeks. In the female—the reaction was less marked and of shorter duration here—it was noted between the eleventh and seventeenth weeks. At the end of twenty weeks, this fuchsinophilic staining reaction normally disappeared. In addition, Vines found this stain taken up by the acidophile cells of the pituitary, the interstitial cells of the testis, and the cells of the young corpus luteum. In 1934, Broster reported a series of fifteen cases of the adrenogenital syndrome in which he described the fuchsinophilic reaction in nine of them as strong, in three of them

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Fig. 1.—Facies of Cushing's syndrome.

as moderate, and in the remaining, as fairly marked. He divided the cases of adrenogenital syndrome into three types: In Group I were included the cases of adrenopseudohermaphroditism; in Group II were included the cases of adrenal virilism—changes were noted after puberty; in Group III were included the cases of mild virilism. Of Broster's fifteen cases, eleven belonged to Group II. Following a unilateral adrenalectomy, there was a moderate improvement in most of these patients. The male characteristics disappeared, the menses became regular, and there was a disappearance of the hirsutism. As the result of the work of Broster and Vines, it was felt that a special staining reaction associated with clinical masculinization of the female had been discovered, and the staining reaction was present temporarily in the cells of the adrenal cortex of both sexes in the early stages of fetal life. The case presented here corroborates the work of Broster, Vines and other investigators, in that a rather marked fuchsinophilic staining reaction was noted in the adrenal resected.

CASE REPORT

Mrs. G. M. was admitted to St. Joseph's Hospital Sept. 16, 1946, and discharged Oct. 25, 1946. On admission, the patient was complaining of dryness of the skin, increase of hair on the body, and insomnia. She stated that in March, 1945, she had noticed the first symptoms, which she described as a bloating of the stomach and insomnia, increasing in severity as time went on. In July, 1945, she was told by her mother that she was gaining in weight, and that it was particularly pronounced in the face, neck, and shoulders. She also noticed, at this time, that the hips and legs were reducing. In January, 1946, the obesity of the face, neck, and shoulders became conspicuous, and, in addition, her hair began to thin out and became very dry. However, at this time, she noticed hair appearing on the face, arms, legs, back, and buttocks. It was at this time that the menses, which had previously been scanty and irregular, ceased entirely. In January, 1946, the skin gradually became coarse and scaly and she also noted a marked diminution of libido while the breasts were becoming atrophic. Three months prior to hospital admission, she developed a marked back pain which persisted up to the time of admission. Her father and mother were living and well, as were three sisters and one brother. The patient had a tonsillectomy at the age of 14 years. There were no other serious injuries or diseases; past history revealed she had had a normal pregnancy in 1941, with the delivery of a normal female child.

Physical Examination.—The general appearance revealed a well-developed, well-nourished, white woman. The skin of the entire body appeared scaly and rough. There was a male distribution of hair except on the chest. Examination of the pupils revealed reaction to light and accommodation. The ears, nose, and throat appeared normal. The hair of the scalp appeared to be thin, and the scalp scaly. Examination of the chest showed the lungs clear to auscultation and percussion. The neck and shoulders appeared to have much fat. A hump was noted between the scapulae. The breasts appeared atrophic. Examination of the heart revealed the tones to be clear, the rate and rhythm regular. No murmurs were heard. The blood pressure was 180/110. Examination of the abdomen did not reveal any palpable masses. Examination of the extremities revealed an unusual amount of hair on both arms and legs. The reflexes appeared normal.

Laboratory Findings.—On admission to the hospital, a urinalysis showed the specific gravity to be 1.008. The remainder of the examination was negative. On September 26, the blood calcium was 8.7 mg. per 100 c.c. The blood serum potassium was 45.4 mg., the acid phosphatase 1.83 units, the alkaline phosphatase 20.85 units (King-Armstrong units). On October 18, the blood serum potassium was 39.7, the acid phosphatase 1.5 units, the alkaline phosphatase 13 units (King-Armstrong units).

In March, 1946, the patient was registered in Ancker Hospital, St. Paul, at which time other laboratory work was done. A glucose tolerance test, at this time, revealed a fast-

ing blood sugar to be 170 mg. per cent. The first hour was 235, the second hour 308, the third hour 311, the fourth hour 242 mg. per cent. On another occasion, the fasting blood sugar was reported as 178 mg. per cent. A spinal fluid examination revealed the pressure to be 160 mm. water. The total protein was 72.2 mg. per 100 c.c. and the Wassermann and the colloidal gold were negative. The hemoglobin was 13.8 Gm. per 100 c.c., the leucocyte count 11,350 with polymorphonuclears 87 per cent, lymphocytes 11 per cent, and monocytes 2 per cent. A blood cholesterol was 269 mg. per cent. The blood chlorides were 620 mg. per cent. On April 10, 1946, a 17-ketosteroid determination on a twenty-four hour urine was reported as 11 mg. The basal metabolism was minus 23 per cent and the Van Slyke 67 volumes per cent.

Fig. 2.

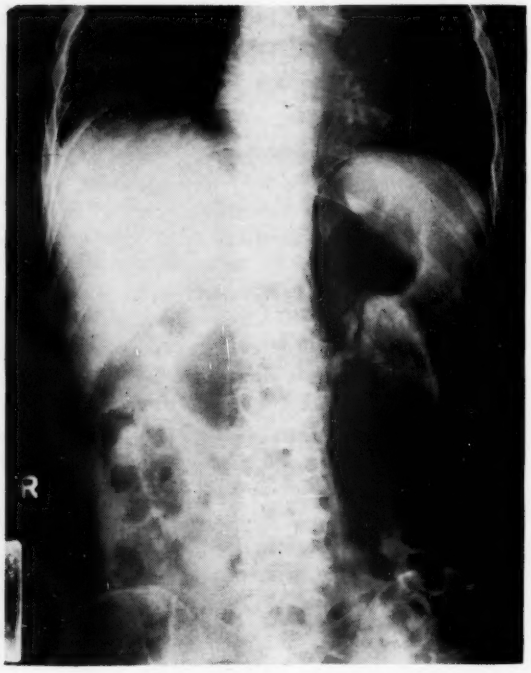

Fig. 3.

Fig. 2.—Air injected right renal area.
Fig. 3.—Air injected left renal area.

X-Ray Findings.—In March, 1946, while the patient was at Ancker Hospital, roentgenograms of the chest and skull were reported as negative. On admission to St. Joseph's Hospital, air was injected into the left perirenal space and no evidence of tumor could be noted. A few days later, the right perirenal area was examined by the instillation of air and reported as negative to tumor. At this time, fractures of the right ninth rib and the left eighth and ninth ribs anteriorly were noted. These were uniting, and a bony callus was present. Compression fractures of the bodies of the eighth and ninth thoracic and first lumbar vertebrae were also noted, and all the bones showed marked decalcification.

Operation.—On Oct. 5, 1946, an exploratory laparotomy was performed. The ovaries were noted to be somewhat atrophic but the uterus appeared normal. Careful palpation in the pelvis and along the vertebral column and ureters on either side revealed no evidence of tumor. Both adrenals were palpated and because the right adrenal felt larger than the left, and small nodules could be felt on it, one-half of it was resected.

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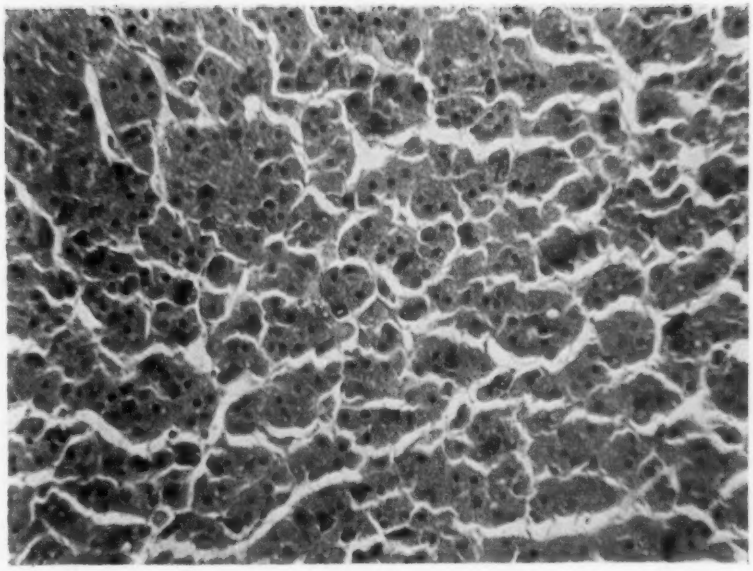
Fig. 4.



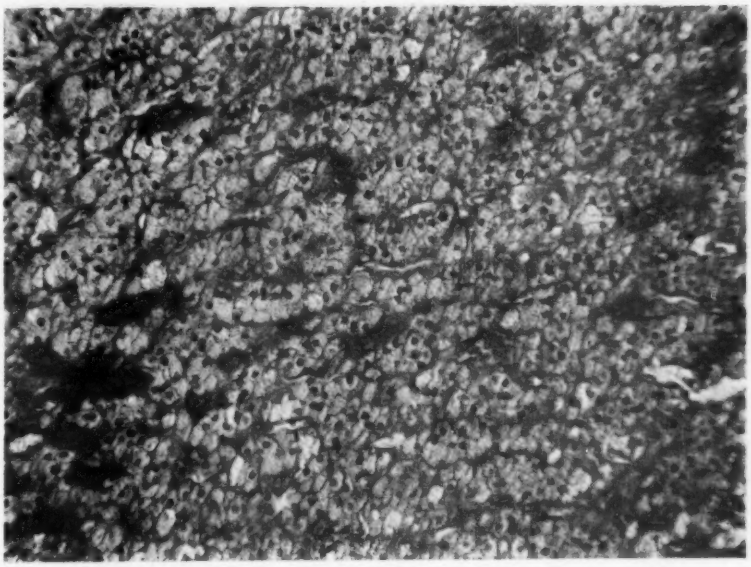


Fig. 5.

Fig. 4.—Normal adrenal stained with Ponceau fuchsin.
Fig. 5.—Patient's adrenal stained with Ponceau fuchsin.

Pathologic Findings.—The adrenal presented no unusual gross abnormalities. Sections were made and stained with the Ponceau fuchsin stain. The technique of the Ponceau fuchsin stain consists in fixation of the tissue in a 2.5 per cent solution of potassium bichromate and a 1 per cent sodium sulfate. The tissue is embedded in paraffin, following which it is stained for five minutes in a solution of 1 part of a 1 per cent acid fuchsin and 2 parts of a 1 per cent Ponceau DeXylidine. It is then washed in distilled water and differentiated for five minutes in a 1 per cent solution of phosphomolybdic acid. The tissue is then placed in a 2.5 per cent solution of aniline blue after which it is washed in distilled water and then differentiated in 1 per cent acetic acid. The tissue is then mounted in balsam. Normal adrenal cells, for the most part, absorb the aniline blue stain. The androgenic cells take up the red acid fuchsin stain. The adrenal, in this case, presented a rather marked fuchsinophilic staining reaction, which was most pronounced in that part of the cortex adjacent to the medulla. In some areas, the fuchsinophilic cells were noted extending from the juxta medullary zone to the zona glomerulosa; such a zone is shown in the photomicrograph (Fig. 5).

Progress in Hospital.—Prior to surgery, the patient appeared emotionally upset and depressed at times. In conversation, her remarks were occasionally incoherent. Following surgery, the patient made an uneventful recovery. She was given deep x-ray therapy to the pituitary, and on Oct. 25, 1946, was sent home. About four weeks after leaving the hospital, she had a small amount of vaginal bleeding and eight weeks after hospital discharge she had a normal menstrual period—the first in almost two years. At the time of this communication, there had been a moderate improvement in mental condition.

SUMMARY

A case of Cushing's syndrome is reported in which the only significant pathologic finding is a rather marked fuchsinophilic staining reaction in the adrenal. The same stain applied to the controls did not reveal this degree of fuchsinophilic staining reaction.

Following surgery, which must of necessity have destroyed a greater portion of the adrenal, and x-ray therapy to the pituitary, a definite improvement in the patient's condition has been noted.

There is evidence in the literature, and in this case, that the fuchsinophilic staining reaction often referred to as the androgenic zone bears a direct correlation to the degree of masculinization in the female. However, no claim is made that this staining reaction, representing a hyperplasia of the androgenic zone, is the only etiologic factor in the case. The possibility that these fuchsinophilic cells may be a by-product of some other vital process, as well as the role of the pituitary, must still be considered.

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RADICAL PANCREATODUODENECTOMY WITH RESECTION OF THE PATENT PORTAL VEIN

An Experimental Study

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TUMORS in and about the head of the pancreas yet stand as a challenge to the surgeon. These lesions usually produce symptoms early and thus should be most favorable for surgical treatment. This is not the case. Great strides have been made in our attack on this problem but a cure of carcinoma of the head of the pancreas remains a rarity. The reason for this seeming paradox lies in the anatomic relationship of the structures in this area, chief among which is the close proximity of the portal vein to the intrapancreatic portion of the common bile duct. Although these tumors when small in size involve the bile duct producing obstructive jaundice, even this early they have usually likewise involved the pancreatic tissue about the portal vein if not the vein wall itself. The surgeon approaching such a tumor is beset by a problem which uncommonly can be solved by existing methods. If his technique is radical enough to remove the tumor adequately he is likely to damage vital blood vessels. On the other hand, cautious sparing of these structures too often leads to incomplete removal of tumor tissue. It seemed to us that adequate treatment of these lesions necessitates resection of the portal vein.

It has long since been shown that neither the duodenum nor the head of the pancreas is necessary for maintenance of life. As early as 1877 von Eck had successfully performed his later famous Eck's fistula in dogs.[1] He was able to ligate the portal vein and anastomose it to the vena cava with survival of the animals. Many variations of his technique have been used both experimentally and clinically. Whipple[2] and Blakemore[3] have recently reported the successful use of a vitallium tube in anastomosis of the portal vein to the vena cava in the treatment of portal hypertension. Thus, both experimental and clinical investigations indicate that the portal vein need no longer be considered vital if its blood be shunted into the systemic venous circulation. We have been studying the possibility of combining the present-day techniques of pancreatoduodenectomy with portal vein resection, the continuity of the venous return from the bowel being re-established by the use of a superior mesenteric-vena caval shunt.

METHOD

First, six healthy adult dogs were subjected to portal vein ligation with implantation of its distal cut end into the vena cava immediately above the renal veins. The dogs were anesthetized with intraperitoneal injection of sodium

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TABLE I. RESULTS OF OPERATIONS

DOG NO.	ANESTHESIA	TRANSFUSION	SURVIVAL	COMMENT
		Group I. Portal Caval Shunt		
253	Nembutal	None	94 days	Sacrificed in good health after weight gain; vessel anastomosis patent without thrombosis
454	Nembutal	None	140 days	Living in good health
380	Nembutal	None	128 days	Sacrificed because of severe mange; no weight loss; vessel anastomosis patent with small nonobstructing mural thrombus in cava
406	Nembutal	None	1 day	Inadequate postoperative care; vessel anastomosis patent without thrombosis
473	Nembutal	None	12 days	Sacrificed because of persistent vomiting; had an ileo-ileal and an ileo-cecal intussusception; anastomosis patent without thrombosis
691	Nembutal	None	5 days	Generalized peritonitis; bowel normal; anastomosis patent without thrombosis
		Group II. Pancreatoduodenectomy With Portal Caval Shunt		
432	Nembutal	None	47 days	Died after marked weight loss; had multiple jejunal ulcerations with perforation and peritonitis; vessel anastomosis patent without thrombosis
592	Nembutal	None	12 hr.	Died without recovery from anesthetic; hepatic artery ligated; vessel anastomosis patent without thrombosis
526	Nembutal	None	1 day	Died without recovery from anesthetic; vessel anastomosis patent without thrombosis
202	Nembutal	None	2 hr.	Died in shock with marked blood loss into stomach and spleen after ligation of the splenic vein; anastomosis patent without thrombosis
492	Nembutal	None	0	Died before completion of operation
460	Nembutal	None	3 hr.	Died without recovery from anesthetic; vessel anastomosis patent without thrombosis
420	Nembutal	None	0	Died before completion of operation
430	Nembutal	400 c.c. whole blood	0	Died immediately after operation; vessel anastomosis patent without thrombosis
448	Ether	200 c.c. whole blood	1 day	Died after convulsions; vessel anastomosis patent without thrombosis; no gross anatomic cause for death
558	Ether	None	7 hr.	Died without recovery from anesthetic; hepatic artery ligated; vessel anastomosis patent without thrombosis
461	Ether	None	2 days	Cholangitis with liver abscesses; vessel anastomosis patent without thrombosis
381	Ether	None	4 hr.	Died in shock; portal vein kinked over vitallium tube with congestion of stomach, spleen, and intestine; no thrombosis
597	Ether	600 c.c. whole blood	84 days	Died after terminal weight loss; had four jejunal ulcers; vessel anastomosis patent without thrombosis
644	Ether	400 c.c. whole blood	1 day	Died, aspiration bronchopneumonia; obstruction of cholecystojejunostomy; vessel anastomosis patent without thrombosis
598	Ether	500 c.c. whole blood	1 day	Died, bronchopneumonia; bile peritonitis from cholecystojejunostomy leak; vessel anastomosis patent without thrombosis

TABLE I—CONT'D

DOG NO.	ANESTHESIA	TRANSFUSION	SURVIVAL	COMMENT
468	Ether	300 c.c. Whole blood	1 day	Died; bile peritonitis from cholecystojejunostomy leak; vessel anastomosis patent without thrombosis
443	Ether	300 c.c. Whole blood	7 days	Died; animal refused to eat and had distemper; vessel anastomosis patent without thrombosis
70	Ether	250 c.c. Whole blood	3 days	Died; early peritonitis; obstruction of cholecystojejunostomy; cholangitis with liver abscesses; vessel anastomosis patent without thrombosis
587	Ether	200 c.c. Whole blood	2 days	Died; at operation dog had advanced cirrhosis of liver; vessel anastomosis patent without thrombosis
399	Ether	150 c.c. Whole blood	5 days	Died; distemper and generalized peritonitis; bowel normal; vessel anastomosis patent without thrombosis
573	Ether	None	12 hr.	Died in shock; vessel anastomosis patent without thrombosis
544	Ether	600 c.c. Whole blood	34 days	Died; perforated jejunal ulcer with peritonitis; vessel anastomosis patent without thrombosis

pentobarbital, .032 Gm. per kilogram of body weight. The abdomen was entered through a long right rectus incision and the intestines were reflected to the left. The superior mesenteric, splenic, and portal veins were freed by sharp dissection from the surrounding tissues. The superior pancreatoduodenal vein was identified, ligated, and divided. The vena cava and renal veins were similarly mobilized. A rubber-shod umbilical cord clamp was then applied to the origin of the portal vein after which the vein was ligated flush with the liver and divided below this ligature. A Blakemore and Lord tube of appropriate size was ligated on the free end of the portal vein according to their technique.[4] A segment of vena cava was then isolated by application of clamps to the renal veins and to the cava above and below the site of implantation. A defect was made in the anterior wall of the isolated cava within the circle of two previously placed purse-string sutures. The portal vein covered vitallium tube was inserted into the caval aperture and anchored by ligation of these sutures.

Next, twenty-two healthy adult dogs were subjected to the radical combined operation. In this procedure the major part of the pancreas, together with the duodenum and the lower fifth of the stomach, was resected. The distal cut end of the duodenum was infolded with purse-string sutures and the common duct ligated and divided. An end-to-side gastrojejunostomy was established following which the portal vein was ligated, divided, and implanted into the cava as outlined previously. A cholecystojejunostomy was constructed and the abdomen closed without drainage. Sodium pentobarbital anesthesia was used in the first eight animals and ether in the remaining fourteen. All animals were given intravenous infusions of saline solution during the operation and, in addition, the last eleven dogs received whole blood, in amounts varying from 150 to 600 c.c. Postoperatively, animals which survived more than a few hours received parenteral saline and dextrose solutions. All animals were given postoperative injections of sodium penicillin, 10,000 units every five to six hours.

RESULTS

The results of these operations are summarized in Table I.

The anastomosis remained patent without thrombosis in all six of the animals with a simple portal caval shunt. Three of these animals survived for long periods and were sacrificed. One died in the first postoperative day, apparently from lack of adequate postoperative care. One died on the fifth postoperative day and at autopsy was found to have an extensive suppurative

Fig. 1.—Multiple stomal ulcerations found at autopsy of Dog 432, forty-seven days after operation.

peritonitis, presumably the result of skin contamination of the peritoneal cavity at the time of operation. The last animal died on the twelfth postoperative day and at autopsy was found to have a complicated intussusception which had resulted in intestinal obstruction.

The first eight dogs subjected to combined pancreatoduodectomy and portal caval shunt were anesthetized by intraperitoneal injections of sodium pento-

barbital. Of this group seven died within the first twenty-four hours after operation without regaining consciousness. The remaining dog lived for forty-seven days.

The last fourteen dogs received ether by inhalation. The first four animals of this group regained consciousness but all died within the first forty-eight hours, one with occlusion of the hepatic artery, one as the result of kinking of the superior mesenteric vein, one with cholangitis and liver abscesses, and one following a series of convulsions. Nine of the remaining ten dogs were transfused with whole blood during operation. Seven of these animals received an average of 300 c.c. of whole blood but all died during the first week, three as the result of extensive bronchopneumonia, two with distemper, one with obstruction of the cholecystojejunostomy stoma, and one because of previous liver disease. Two dogs of this last group received 600 c.c. of blood each and each made an uneventful recovery from the operation, living for thirty-four and eighty-four days, respectively.

Fig. 2.—Appearance of anastomosis in Dog 597, eighty-four days after operation. The posterior wall of the vena cava has been incised to expose the well-healed anastomosis in its anterior wall. The lumen of the superior mesenteric vein appears much reduced because of lack of attachment.

Each of the three long-surviving dogs developed stomal ulcerations and died as a result of this complication (Fig. 1). Two developed frank perforation with generalized peritonitis, and the third died after a period of persistent vomiting, marked dehydration, and emaciation. Obstruction of the portal caval shunt occurred in only one animal in the entire series and this resulted from kinking of the mesenteric vein. The remainder of the vessel anastomoses healed

cleanly and remained patent (Fig. 2). The one exception to this was the single occurrence of a small mural thrombus which produced no obstruction of the vena cava.

COMMENT

Surprisingly enough, anastomosis of the portal vein to the vena cava caused relatively few early local or general complications and the few which did occur were directly traceable to faulty technique. Apparently sufficient impairment of hepatic function occurs to make barbiturate anesthetics contraindicated in this work. Ether proved to be a satisfactory anesthetic agent. That blood loss into the visceral circulation during portal vein occlusion and into the inferior systemic circulation during caval occlusion is of considerable amount is borne out by the necessity for transfusion of large volumes of whole blood. In all probability a few animals could have been salvaged by more adequate postoperative care, although blood transfusions during operation seemed to be the most important single factor influencing survival. The fact that all three of the dogs which survived for a considerable period had extensive gastrojejunal ulcerations would seem to indicate the need for more extensive gastrectomy or vagotomy as part of the procedure.

The results observed in these animals although disheartening are yet promising enough to warrant further investigation. The most important factors in successful instances seem to have been careful surgical technique, adequate whole blood transfusion during operation, and careful postoperative care.

CONCLUSIONS

A radical pancreatoduodenectomy with portal vein resection has been shown to be possible in the dog. Its complications have been tabulated.

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A METHOD OF CRANIOPLASTY USING READY-MADE ACRYLIC CRANIOPROSTHESES

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METHYL methacrylate is a synthetic thermoplastic compound well known to the plastics industry and to aircraft manufacturers as Plexiglas, Lucite, Perspex, Acryloid, or simply, Acrylic or Acrylic Resin. It is less well recognized as a cranioplastic material although it antedates the currently popular tantalum for this purpose.

The usual methods of shaping either tantalum or acrylic into cranioprostheses are fundamentally identical and depend on dental impression techniques. A "ready-made" method of cranioplasty was developed for tantalum[12] to obviate such lengthy and comparatively elaborate procedures, intermediate preparatory craniotomies, and laboratory processing. This proved so satisfactory in a variety of unpredictable situations that acrylic was substituted for the metal, combining the merits of the method with those of, what promises to be, a superior cranioplastic material.

An acrylic hemisphere of fixed radius is formed by pressure-molding the easily obtained acrylic sheet stock. This serves as a basic exemplar whose radius is identical with that of the four major spheroidal surfaces of the skull, all of which possess practically equal radii of curvature.[12] This method of cranioplasty thus, simply and directly, replaces one spheroidal surface (the area of the bony defect) with a basically identical one of transparent plastic. Fig. 1 illustrates the very near duplication of the major skull contours by merely placing a segment of a basic acrylic prosthesis in various positions on a skull. One of these "basics" is routinely sterilized for all cranial operations and provides one, or more, specific prostheses depending on the size of the cranial defect.

This method of cranioplasty is applicable regardless of the extent and location of a skull defect, whether it be of a complex fronto-orbital type or of a simple parietal variety (Fig. 2). No special instruments or tools are required and but a single item of easily constructed, homemade equipment is necessary for shaping the plastic. The procedure for forming a basic cranioprosthesis and the details of its use are described in the paragraphs that follow.

LITERATURE

This remarkable plastic is available as either a molding powder or as commercially cast sheet stock of almost any desired thickness. Both forms of the substance have been used for cranioplasty.

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First utilized for cranial windows in experimental rabbits because of its unique optical properties,[10] Zander was the first to use acrylic in human cranioplasty, in October, 1940. The prosthesis for the large left frontal defect in his one case was form-molded over a plaster replica of the wanting bone.[10]

Walker and his group (Taggert, Lambros, and Woolf) began using acrylic for human cranioplasty in 1941,[7, 11, 16] and followed the form-molding technique after first processing their own plastic plates. Gurdjian, Webster, and Brown essentially duplicated Zander's technique in their case the next year[4] and Kahn also employed it in four of his cases but failed to mention the method used.[7]

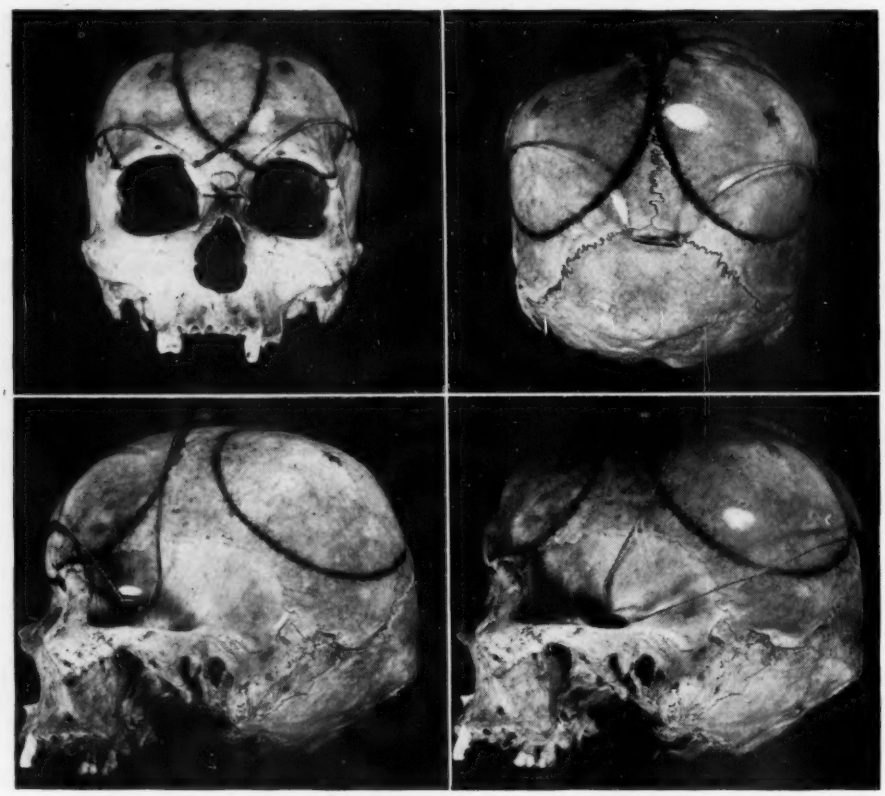

Fig. 1.—Conformity of a half segment of a basic acrylic cranioprosthesis variously positioned on a skull showing the four major spheroidal surfaces of equal radii.

Subsequently, Walker and associates developed a denture-construction technique[16] wherein a mold and counter mold of a defect are obtained through the intact scalp and the acrylic is then polymerized between the two from the molding powder (and liquid monomer). After polishing, this process yields a transparent, tailor-made cranioprosthesis. Kerr briefly referred to a similar procedure as employed by him in seven cases.[9]

In 1945, Small and Graham reported twenty-five cases of acrylic cranioplasty in which they followed a modification of Walker's denture technique.[15] The molds of a cranial defect were made directly at a preparatory craniotomy; then, after processing in the laboratory, the prosthesis was inserted at a second

operation. This technique is also described in the recent paper by Elkins and Cameron on the work begun by J. M. Cameron and totaling seventy cases.[3] Independently, both groups of surgeons have shortened the laboratory processing time of the plastic to the extent that their technique is now a lengthy but one-stage procedure. The original two-stage method has been successfully applied to the production of entire acrylic calvaria for experimental monkeys by Sheldon, Pudenz, Restarski, and Craig.[14]

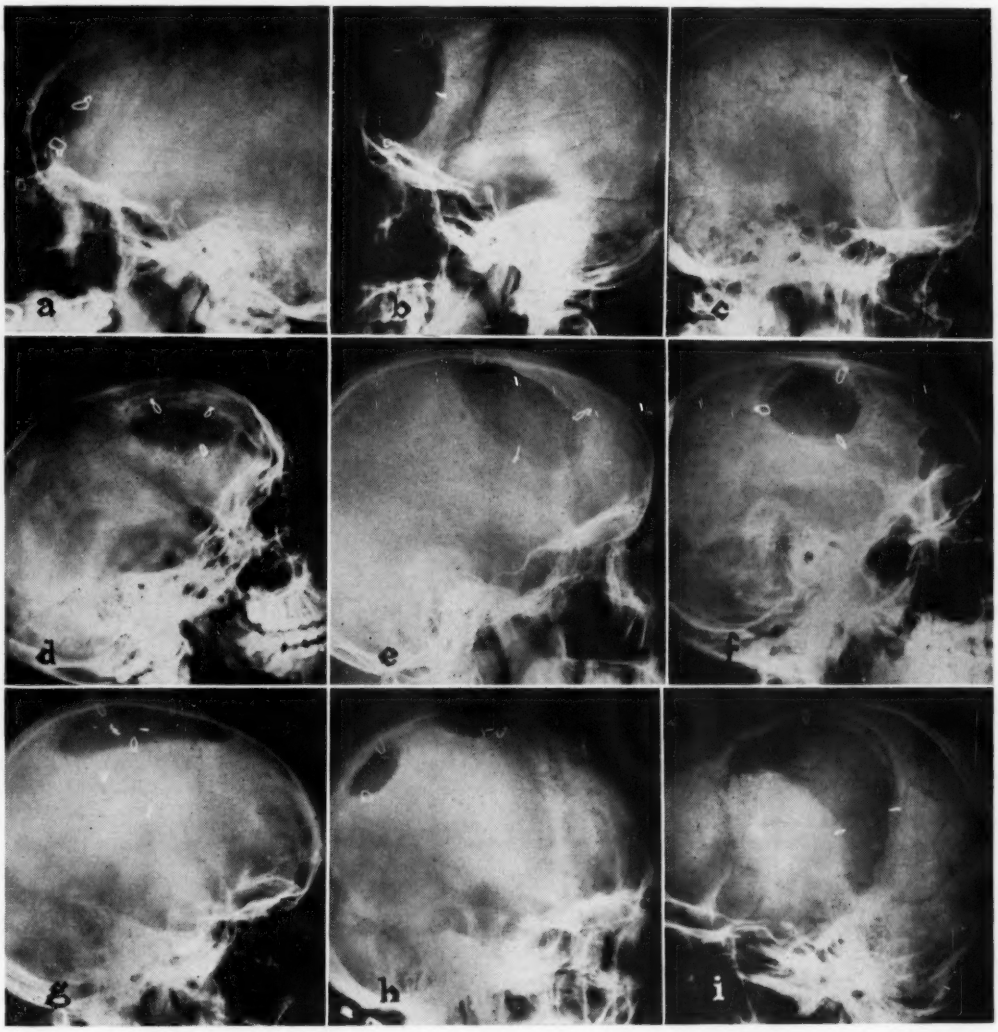

Fig. 2.—Postoperative roentgenograms. The position of the radioparent acrylic in the defects is marked by the tantalum ribbon anchorings. *a* and *b*, Fronto-orbital prostheses; *c*, *d*, and *e*, frontal prostheses; *f*, *g*, and *h*, parietal and frontoparietal prostheses; *i*, large frontotemporoparietal prosthesis.

These comparatively elaborate technical methods are all productive of accurate cranioprostheses but lack the very obvious advantages of equally, or more, accurate ready-made methods as designed for vitallium,[1] tantalum,[12] and now for acrylic cranioplasty.

PRESSURE-MOLDING EQUIPMENT

One of the most spectacular physical properties of methyl methacrylate is its "elastic memory"—the material permits molding into almost any shape when heated, reverting back to its initial conformation when reheated.[13] In common with all other thermoplastics, acrylic experiences a physical change only, when heated to its molding temperature.[8] These propensities allow this material to be shaped by one, or more, of three different molding processes: (1) pressure molding (blowing), (2) vacuum molding, or, (3) form molding. All of the cranioprostheses employed in this present series of seventeen cases were formed by the pressure (blow)—molding method. After extensive experimentation, the prostheses produced in this manner consistently proved to be the most perfect, the most easily and most rapidly formed.

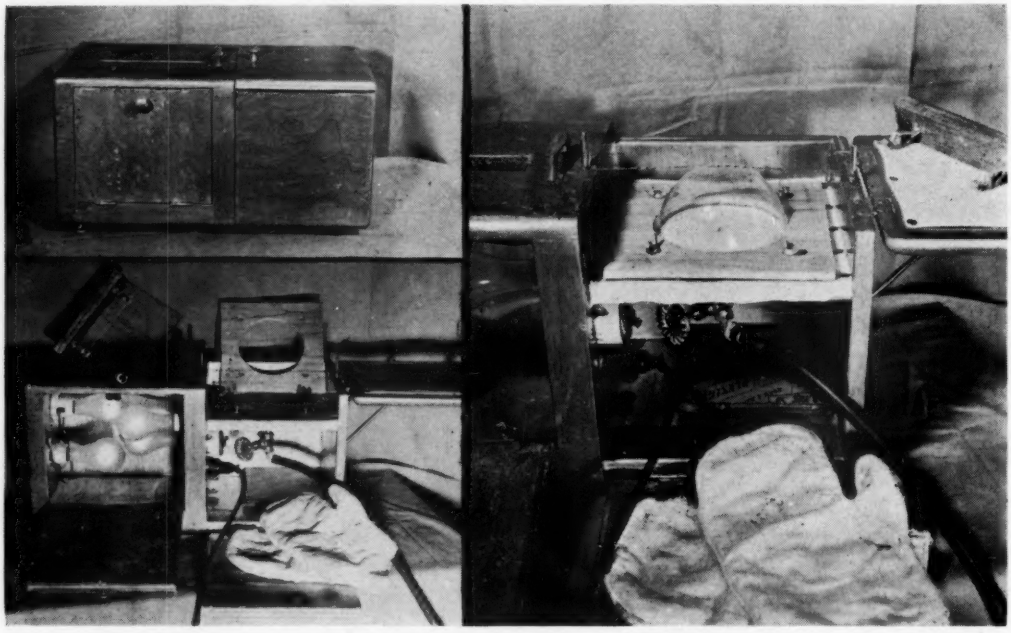

Fig. 3.—Pressure molding unit. *a*, Unit closed for carrying; *b*, unit open and ready for molding (heating unit opened to show insertion of acrylic between incandescent globes); *c*, the blowing unit containing a newly formed "bubble" contacting the horizontal thread and showing the pressure line and valve.

A pressure-molding unit may be assembled in a few hours and, like my original crude and unfinished equipment, need not be as elaborate as the portable 'bubble box' illustrated in Fig. 3, *a*. A heating unit and a blowing unit are conveniently combined in a plyboard box with ample carrying space for accessories and sheets of acrylic.

The heating unit (Fig. 3, *b*) may be any device for developing a temperature of about 275° F. whether this be ordinary incandescent or infrared globes, the kitchen oven, a Bunsen burner, or heating elements. By and large, oven type heating is the most satisfactory and four 100 watt globes, so arranged that the sheet plastic can be suspended between them, provides adequate and even heating.

The blowing unit (Fig. 3, *b* and *c*) is simply a flat surface (forming table) containing a countersunk pressure outlet, a template (forming ring), and an adequate clamping device. The template is plyboard with a cutout circular center of 2½ inch radius centered over the pressure outlet in the forming table. Four fixed bolts with wing nuts securely batten the template and heated acrylic down to this surface. Flannelette (or thin felt) is used to cover the forming table (and the attached working table) to prevent blemishes in the heat-softened acrylic as any defect in a contacting surface, however infinitesimal, is assuredly transferred to the material. This plastic duplicates a surface, whether a defect or a polish. Likewise, the use of flannelette mittens spares both the plastic and the hands.

A thread tightly stretched between two upright posts and across the pressure outlet at a height of 2½ inches (Fig. 3, *c*) gauges the vertical radius of a prosthesis during its molding. This radius equals that of the template. Although the major skull prominences possess a common of radius of 2¼ inches,[12] within negligible differences, the thickness of the plastic and the mechanical discrepancies in forming it necessitates this slight increase in radius to produce a basic prosthesis of the proper mensuration.

Carboys of carbogen, oxygen, carbon dioxide, or compressed air provide adequate pressure. About 100 pounds of pressure per square inch is ideal and a small hand valve inserted in the pressure line offers instant control. Automobile fuel-line tubing and fittings suffice where metal parts are used. Rubber pressure tubing, from the carboy to the valve, obviates a blowout and threaded (or wired) unions prevent slipped connections.

In actual production, this equipment yields a basic cranioprosthesis every four minutes so that a long-time supply can be molded in the course of one or two hours. Also, by varying the size and shape of the template opening, the acrylic can be molded into diverse forms serving many purposes so that the molding unit does possess some versatility.

PRESSURE-MOLDING TECHNIQUE

Commercially cast sheets of acrylic (said to be more chemically inert than that processed from molding powder[8]) are marketed in practically any thickness. The 3/32 inch sheet is the most satisfactory for the purpose at hand, retaining a thickness of about 1.5 mm. after molding. Sheets of 2/32 or 4/32 inch thickness may be used if thinner or thicker prostheses are desired. This material is readily obtained at low cost in hobby marts and most novelty shops.

A 6 by 6 inch square of sheet acrylic is suspended in the heating unit after removing the protective adhesive paper from both of its surfaces. It quickly acquires a "wobbly" flexibility and is then rapidly placed on the forming table and secured under the template. As the pressure valve is slowly opened, the heated plastic expands into a bubble or blister (Fig. 3, *c*). When its summit contacts the horizontal thread the flow of gas is reduced enough merely to maintain contact between the two, until the material cools.

Basic prostheses formed in this manner suggest a transparent derby hat with a square brim (Fig. 4). The crown is cut from the brim about ¼ inch above their junction. Several of these may be formed at one time and stored for future use without change in shape or chemical composition. The flat remnants may be salvaged for making acrylic cement.*

Any imperfect bubbles may be returned to the heating unit where the plastic will resume its initial flatness ("elastic memory") and can be molded again—there is thus no loss or waste. Too great, too little, and sudden blasts of pressure should be avoided. One should strive for even heating of the plastic, remembering that suddenly liberated gases have a cooling effect—the material should be heated to the extent that it has the flexibility of moistened blotting paper before removing it from the oven.

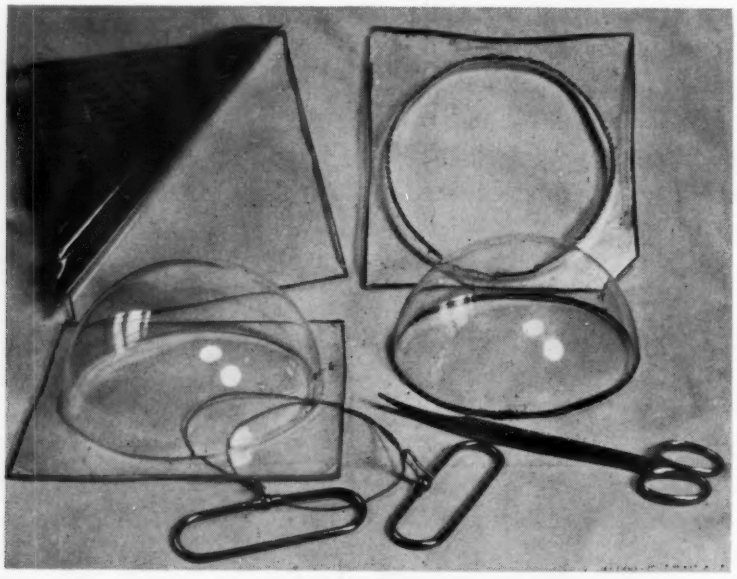

Fig. 4.—Sheet of acrylic, a newly formed bubble, and a completed basic prosthesis.

Although the forming equipment is inexpensive and simple of construction and operation, commercially produced basic cranioprostheses would add little to the cost but something to convenience, should this ready-made method of cranioplasty find favor. The acrylic arthroplasty cups used by some orthopedic surgeons are provided in this manner.[5, 6]

Despite a soft surface, acrylic is a rugged and tough substance which, in the thickness used for cranioplasty, has working qualities comparable to lead. A Gigli saw or curved dissecting scissors readily cuts a prosthesis (Fig. 4) as will the actual cautery, although the characteristic "acetic" odor evolved may be objectionable. Motor-driven saws and router-type instruments common to neurosurgical and orthopedic operating rooms work this plastic admirably. Any small hand drill suffices for forming holes in the material.

*Acrylic shavings dissolved in ethylene dichloride or in acetone form an excellent cement for welding pieces of plastic together, for impregnating cotton or silk sutures and for liquid adhesive in applying small dressings.

TECHNIQUE OF CRANIOPLASTY

Each basic cranioprosthesis is thoroughly washed in warm, soapy water (not hot water) then sponged with ether and alcohol immediately prior to sterilization. This treatment removes any of the adhesive remaining on the plastic from its protective paper and permits sterilization by immersion in solutions. While sterilization in 1:1000 mercuric oxycyanide has averaged about two hours in my cases, a one hour treatment is probably sufficient.[6] A one hour exposure in 0.1 per cent mercuric chloride has been recommended[6] as well as twenty-four hour immersion in 95 per cent alcohol[4] or fifteen minute sterilization in Bard-Parker solution.[3] It is very important that the solution be agitated occasionally to disrupt air bells adhering to the surface of the plastic and a prosthesis must be thoroughly rinsed with sterile water or saline solution (not hot) before use. Autoclaving or boiling are impossible, of course, unless a suitable mold is made.

The edge of every bony defect is rongeured until viable bone is encountered whether a primary or a secondary repair is being performed or an onlay or inlay type of cranioprosthesis contemplated. In the usual case, the surrounding bone is secure and tolerates the slight trauma of rabbeting which permits the more desirable inlay type of prosthesis (Fig. 5, *a* and *b*). The rabbet (shelf, mortise, or rout) is formed with a ¼ inch shoulder and a depth corresponding to the thickness of the prosthesis. Any flat chisel will suffice although a rabbeting chisel facilitates this step.[12]

The operator can directly trace the margins of a bony defect with bone wax on a segment of a basic prosthesis placed over the area, or a piece of lead foil (cottonoid will do) may be digitally crimped along the bony margin, cut out, and then outlined on the plastic (Fig. 6). In either case, the desired section of acrylic is removed and will be found to conform to the surrounding skull contours in all major respects.

Minor secondary adjustments and alterations are necessary only in the frontoorbital areas or when a defect includes an area of both greater and lesser curvature. Acrylic lends itself well to manipulations of this kind. A basic cranioprosthesis supplies the fundamental over-all curvature while an edge or corner of a cutout segment may be dipped in hot water (from the autoclave) and easily molded with the fingers as desired. A little experience renders this material almost as easily worked as modeling clay and one can readily duplicate missing contours such as an orbital plate or a supraorbital ridge (Fig. 2, *a and b*).

It may occasionally be desired to obliterate a dead space under a prosthesis or compensate some soft tissue deficit. Scraps of sterile acrylic are readily cemented to a prosthesis for this purpose with acrylic cement, acetone, or glacial acetic acid.

Any of the nonabsorbable suture materials may be used to secure a prosthesis to the bone since acrylic is a nonmetal and there is, therefore, no electrochemical hazard. Cotton suture was employed in the first of my cases, while tantalum ribbon anchorings were used in the remainder. Silk[11, 16] and steel wire[3, 4] have been used and Sheldon and associates secured their lucite monkey

calvaria with tantalum or vitallium screws.[14] Tantalum wire would also serve although tending to bite into the plastic when tightly cinched. Some depend solely on pericranium sutured over a prosthesis to retain it in position.[15] Should the surgeon prefer to employ plastic materials throughout, either plastigut[2] or nylon suture may be used.

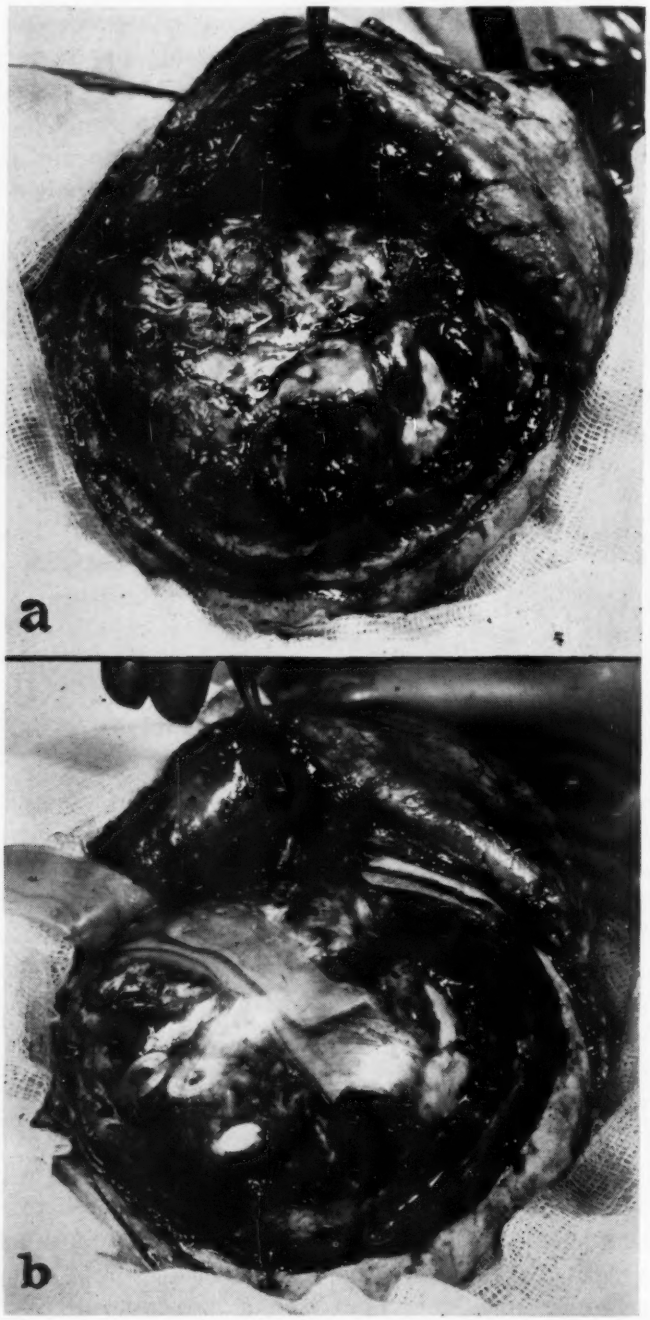

Fig. 5.—A skull defect and an inlay type acrylic prosthesis. *a*, The defect rabbeted and prepared for the prosthesis; *b*, the acrylic inlay anchored in place with tantalum ribbons (a length of rubber dam was placed under the plastic to accentuate the photograph).

Both the onlay and the inlay types of prostheses are anchored in the same manner via matched holes in the prosthesis and through one or both tables of the skull. Two to four pairs of holes are ordinarily sufficient. The suture material is threaded through each pair and then tied or twisted. Once a prosthesis is firmly fixed in position, the cut ends are bent upon themselves and turned down into the holes in the bone (Figs. 2, *a* and *e* and 5, *b*). A prosthesis should never be forced to fit even though it is reasonably flexible—the plastic should always conform to the defect to avoid needless stress on both the material and the bone.

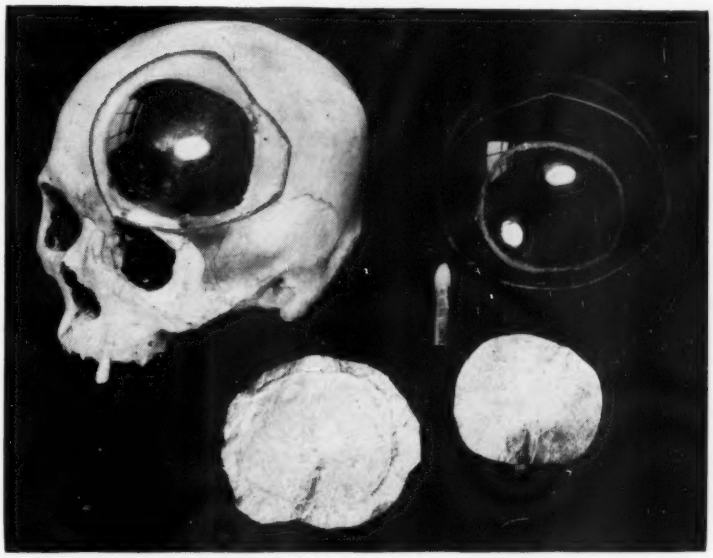

Fig. 6.—A defect may be traced directly on a segment of a basic prosthesis with bone wax, or a lead foil pattern may be made and similarly outlined.

The scalp is sutured in the usual manner after suturing the pericranium if a sufficient amount of this structure remains. A single Penrose drain is routinely placed in a dependent position under the scalp and is not removed until the third or fourth postoperative day, thereby obviating fluid collections.

Neither sulfa drugs nor penicillin have been applied locally during closure as a routine practice.[3, 15] Neither have any of the cranioprostheses used in my cases been perforated to allow egress of fluid or to coax granulations from the scalp, this being proved unnecessary in work with tantalum.[12]

The routine head dressing consists of quantities of well-fluffed sterile gauze under two snugly applied elastic bandages. Except for the one removal necessary for extraction of a drain, the wounds are not dressed until time to remove the sutures.

MATERIAL

This method of ready-made acrylic cranioplasty has been employed 18 times in 17 patients (one patient, Case 4, harbored two defects) since Jan. 11, 1946. The regional distribution included 4 fronto-orbital, 3 frontal, 7 parietal, and 4 fronto-temporoparietal defects (Fig. 2). Eight of the cases were compound comminuted fractures repaired in six hours, one, three, and four months

and two, three, four, and nine years after injury; 5 cases were skull tumors repaired primarily; 3 cases were operative defects resultant from sacrifice of a bone flap, and 1 case was a rapidly enlarging frontal pneumosinus dilatans. All received the inlay type prosthesis.

In no instance was cranioplasty the major indication for operation. The clinical aspects of these cases and the merits of acrylic are considered in a second paper now under preparation, however.

RESULTS

In general, the use of acrylic made cranioplasty an appreciably faster and easier procedure than when employing tantalum. The ready-made method proved satisfactory and the repairs were accepted as technically and esthetically gratifying in each case. The one fatality was not attributable in any way to either the cranioplasty, the material, or the method. Convalescence proceeded uneventfully in the remaining cases and the scalp was firmly adherent to the prosthesis within a period of two weeks.

SUMMARY

1. The rationale, procedure for forming, and method of using a ready-made acrylic cranioprosthesis are described.

2. The technique of fashioning and inserting onlay and inlay types of prostheses is presented.

3. The major technical virtues of acrylic for cranioplasty are:

   (a) Its thermoplasticity allows easy and rapid molding and secondary alteration of basic cranioprostheses.

   (b) The characteristic transparency permits accurate visual tracing of skull defects with bone wax.

   (c) It is readily worked with ordinary instruments.

   (d) Its cementing facility provides for plastic replacement of soft tissue and the obliteration of dead spaces.

4. Economically, acrylic is readily obtained at extremely low cost.

CONCLUSIONS

1. The principal advantages of the ready-made method are:

   (a) A ready-made acrylic prosthesis is instantly available at all cranial operations.

   (b) Accurate replacements of any cranial defect are easily and quickly effected.

   (c) Intermediate preparatory craniotomies are avoided.

   (d) The surgeon is independent of lengthy processing techniques, special equipment, technicians, and hospitals providing them.

2. Both the method and the material have proved technically and esthetically satisfactory in a series of seventeen patients harboring cranial defects such as those encountered in civil neurosurgical practice.

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CONDYLAR GROWTH AND MANDIBULAR DEFORMITIES

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THIS report is an analysis of nineteen cases of arrested growth in the mandibular condyles. It is the purpose of this study to emphasize the importance of this area in the development of the jaw as well as in its function.

Mandibular growth results from an intregration of activities in a number of areas. Surface apposition, particularly at the alveolar margin, posterior border of the ramus, coronoid tip and epiphyseal-like growth at the condyle are responsible for major contributions. Concurrently, there is continuous surface remodeling. Normal development of the mandible depends upon synchronous coordination of the growth activities of the various centers. Interference with any one of them may be expected to alter the orderly progression of development. Thus, growth arrests in the condyles reflect themselves as pronounced mandibular deformities.

The histology of the area has been described by Toldt,[19] Sicher,[16] Charles,[6] and more recently again by Sicher and Weinman,[14] Rushton,[15] and others. This center appears in the 50 mm. stage of the embryo and its activity attains peak levels during the prenatal period.

Microscopic examination (Figs. 1, 2, and 3) reveals the presence of three zones: (1) chondrogenic, (2) cartilaginous, (3) osseous. The condyle is capped by a narrow layer of fibrous tissue which contains connective tissue cells and a few cartilage cells. The inner layer of this covering is chondrogenic, giving rise to hyaline cartilage cells which constitute the second zone. There is interstitial proliferation of the cartilage and in the third zone one observes ossification occurring around the cartilage scaffolding. The picture is analogous to that observed in the endochondral epiphyseal ossification of a long bone.

The condylar growth center maintains its activity longer than most other centers in the head, persisting until at least the twentieth year. This provides the forward and downward vector for mandibular growth and contributes as well to increased width of the jaw.

Examination of the condyle in gross specimens taken from Macaca rhesus monkeys which had received injections of alizarin red revealed deep staining, indicative of intensive growth activity.[3] Cephalometric studies tended to confirm these findings.[4]

Disturbance of this area is not uncommon.[1, 5, 9, 10, 12, 13, 17, 18] It may occur as one of the sequelae of a mastoiditis or middle ear infection. Hematogenous

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infections or those which spread from the dental area may localize in the joint and lead to interference with chondral activity or to ankylosis and/or functional limitations. Similar effects sometimes proceed from traumatic injuries resulting in fractures or in disturbance of the bone-forming cartilage. Two of our cases of arrest were associated with a generalized arthritis which had also involved the temporomandibular joint. Jaw deformities in such cases have been reported by Diamontberger (1891) and Ibrahim (1914).[12] More rarely, inactivation of growth results from neoplasms or congenital absence of structure.[11] Endocrine disturbances in animals have been shown to effect condylar growth.[7, 21] An excellent review of the whole subject has been prepared by Rushton.[15]

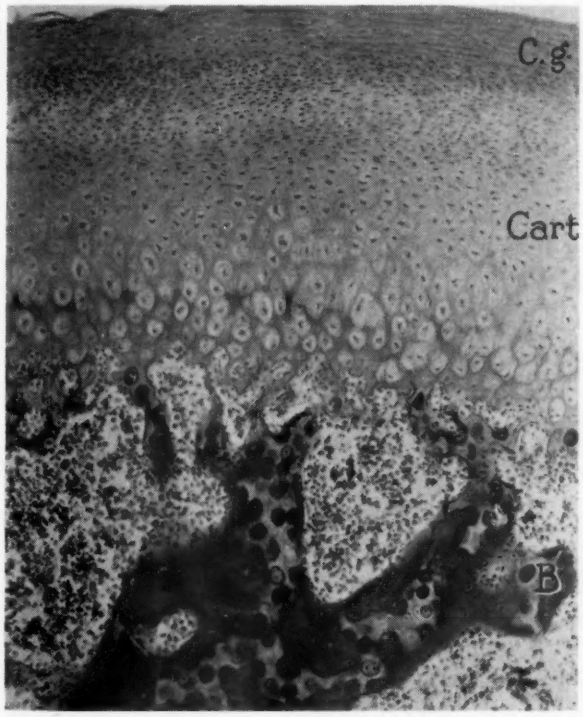


Fig. 1.—Temporomandibular joint area of neonate. Note the three layers described in the text and especially the broad cartilage zone, Orban[14]). *C. g.*, Chondrogenic zone; *Cart.*, cartilage; *B.*, bone.

In a study of normal and abnormal facial growth patterns one of us[5] reported three cases of injury to the condylar center that were analyzed using the technique of Broadbent.[2] (Two of these are included here with further records.) The significance of such disturbances in the production of facial asymmetry was shown by Thompson.[18] (See cases J. G. and R. M. in this report.)

MATERIAL AND METHOD

A series of nineteen cases with history of involvments of the condyle was studied (Table I). Injury of the condyle was determined on the basis

TABLE I. SUMMARY OF DATA IN NINETEEN CASES OF CONDYLAR GROWTH ARREST

CASE	AGE AT PRESUMED ONSET OF ARREST	ASSOCIATED FACTORS	BILATERAL OR UNILATERAL	ORTHODONTIC TREATMENT	SURGICAL TREATMENT	EVALUATION OF FUNCTION	REMARKS
A. C.	Unknown	Unknown	Bilateral	Untreated	None	Function within normal range	Mandible markedly underdeveloped; slight asymmetry with mandibular midline deviated to left
J. F.	Shortly after birth	Polyarthritis with involvement of temporomandibular joint	Bilateral	Untreated	None	Slight limitation of lateral and protrusive range; possible external pterygoid involvement	Mandible markedly underdeveloped; bilateral notching
I. G.	11 mo.	Polyarthritis with involvement of temporomandibular joint	Bilateral	Untreated	None	Slight limitation of lateral movements; other movements within normal range; possible external pterygoid involvement	Mandible markedly underdeveloped; bilateral notching
F. W.	Congenital	Unknown	Bilateral	Treated	None	Normal	Mandible markedly underdeveloped; bilateral notching
A. W.	History not available	Unknown	Bilateral	Untreated	Arthroplasty	Data not available	Bilateral notching
W. U.	13 yr.	Late ankylosis treated by condylar resection at 12 yr.; mandibular deformity occurred subsequently	Bilateral	Treated	Bilateral condylectomy at 13 yr.	Data not available	Bilateral notching
N. S.	9 mo.	Ankylosis	Bilateral	Treated	Left arthroplasty at 14 yr. leading to 1 cm. opening	½ cm. opening with deviation to left; both external pterygoids give evidence of involvement	Some degree of asymmetry; mandible skewed to left; greater arrest in growth on left; bilateral notching
L. R.	Unknown	Unknown	Bilateral	Treated	None	Normal	Mandible markedly underdeveloped; bilateral notching
P. B.	Unknown	Possible early fracture of condyle	Left	Untreated	None	Data not available	Skewed to left; unilateral notching
D. S.	Shortly after birth or congenital	Otitis?	Right	Untreated	None	1½ cm. opening with deviation to right; no left lateral excursion; right external pterygoid involved	Face skewed to right; unilateral notching

J. A.	Shortly after birth or congenital	Otitis at 3 mo. with surgical intervention	Left	Untreated	None	Midline deviated to left on opening; left external pterygoid involved; no right lateral excursion	Congenital absence of left ear canal; mandible skewed to left; unilateral notching
J. L.	Unknown	Unknown	Right	Untreated	None	Opening somewhat limited; midline deviated to right on opening; no left lateral function; right external pterygoid involved	Mandibular left buccal teeth in lingual occlusion; mandible skewed to right; unilateral notching
J. G.	2½ yr.	Ankylosis following infection	Left	Treated	Arthroplasty at 13½ yr.	1 cm. opening increased following surgery; midline deviated to left on opening; no right lateral function; left external pterygoid involved	Mandible skewed to left; unilateral notching
J. M.	Unknown	Unknown	Left	Untreated	None	Data not available	Lower midline skewed to left; unilateral notching
B. G.	2 yr.	Infection and possible otitis	Left	Treated	None	Midline deviated to left on opening; no right lateral function; left external pterygoid involved	Marked skewing of mandible to left; unilateral notching
R. M.	1½ yr.	Involvement of growth center subsequent to infection	Right	Untreated	None	Midline deviated to right on opening; no left lateral function; right external pterygoid involved	Skewing to right; unilateral notching
H. K.	Congenital or 2 yr.	Ankylosis subsequent to birth injury	Left	Untreated	Arthroplasty at 5, 11, 16 yr.	Data not available	Lower right buccal segment lingual to upper; mandibular left buccal segment buccal to upper; 1 cm. opening; unilateral notching
E. C.	8 to 9 yr.	Ankylosis subsequent to dental infection which developed into septicemia and localized in the temporomandibular joint	Right	Treated	Arthroplasty 18½ yr.	Midline deviated to right on opening; no left lateral function; right external pterygoid involved	Unilateral notching
J. B.	14 to 15 yr.	Recurrent mastoiditis which was operated at 15-16 yr.	Left	Treated	None	Limited right lateral excursion; possible left external pterygoid involvement	Slight skewing of mandible to left; mandibular left segment in lingual occlusion; no notching

of (1) history, (2) roentgenographs of the area (cephalometric, laminagraphic, and routine temporomandibular films), and (3) analysis of joint function.

The roentgenographic technique used (Broadbent-Bolton cephalometer) insured consistency of results and the standardization permitted superposition of subsequent film tracings.[2] Laminagraphic and routine roentgenograms of the temporomandibular joint were made in a number of cases.

In eight instances it was possible to follow the same individual serially over periods ranging from one to twelve years. In eight cases the involve-

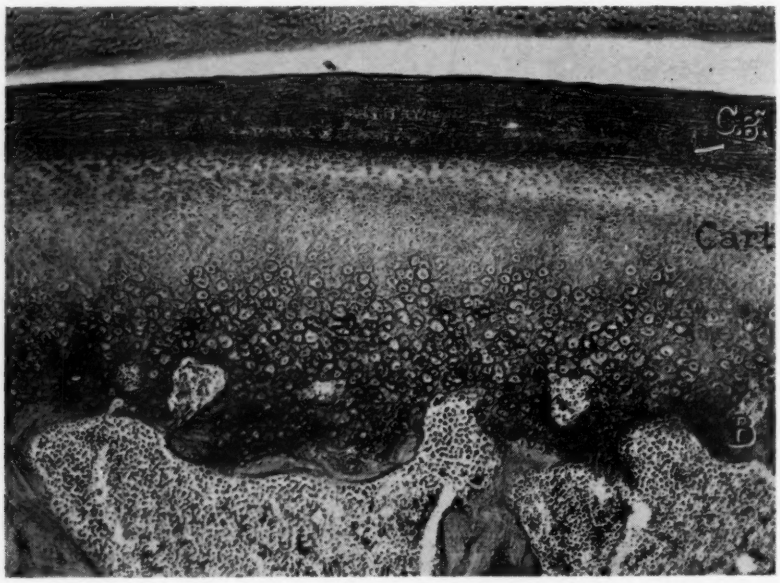


Fig. 2.—Temporomandibular joint area of adolescent (Orban[14]). *C. g.*, Chondrogenic zone; *Cart.*, cartilage zone; *B.*, bone.

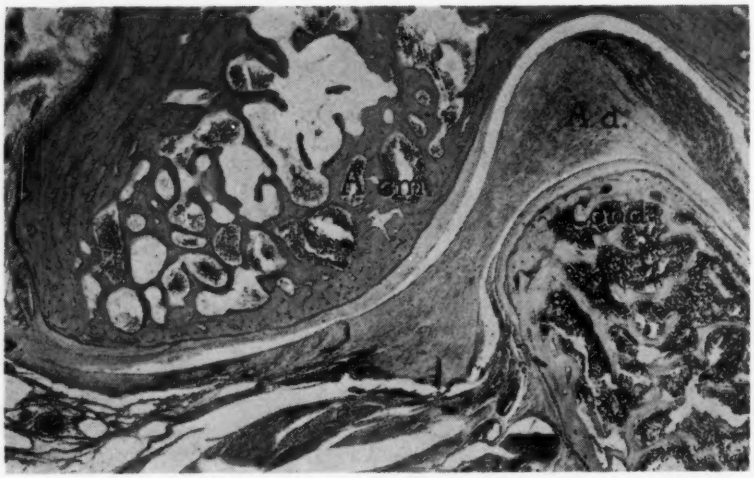


Fig. 3.—Temporomandibular joint area of adult. Note the absence of the zone of proliferating cartilage (Orban[11]). *A. em.*, articular eminence; *A. d.*, articular disc; *Cond.*, condyle.

ment was bilateral. The histories were unfortunately incomplete in many instances. Most of the individuals gave a history of a growth arrest that was early or congenital in origin. In others it was frequently associated with infections and subsequent ankylosis. However, significant functional impairment was not universally present. Orthodontic treatment was attempted in eight cases; six patients had arthroplasties.

For purposes of comparison the tracings of the mandibles of the same individual were superposed using the anterior portion and lower mandibular border as regions of relative stability since apposition and remodeling are minimal there. Measurements were made of the length of the lower

Fig. 4.

Fig. 5.

Fig. 4.—Photograph of D. S. illustrating the characteristic facial deformity occurring in a unilateral arrest. Note the flattening on the unaffected side (left) and the fullness of the right side.

Fig. 5.—Profile photograph of J. F. showing the characteristic facies found in bilateral condylar arrest.

border of the mandible as determined by the distance from gonion to gnathion. The angular relations between the lower border of the mandible and the sella nasion plane, S. N., between the anterior part of the face (N. Gn.) and the sella nasion plane, and between S. Gn. and the sella nasion plane were recorded (Table II, Fig. 15). These were compared with means determined from forty cases of excellent occlusion.[8]

CLINICAL FINDINGS

When there was unilateral involvement (Fig. 4.) the unaffected side usually appeared flat and underdeveloped while the arrested side of the face gave the impression of fullness. The mandible was skewed toward the side of the affected condyle. Palpation of the ramus-body junction generally

TABLE II. SUMMARY OF MEASUREMENTS

CASE	AGE YR.	AGE MO.	LENGTH OF LOWER BORDER OF MANDIBLE (GO. GN.)* (MM.)	ANGLE OF LOWER BORDER OF MANDIBLE TO SN†	ANGLE S.N. GN.	ANGLE N.S. GN.
Control				32.1° ± 4.9°	80.8° ± 3.3°	65.7° ± 3.4°
A. C.	9	4	50	56	64	79.5
J. F.	10	11	46	49	61.5	79
I. G.	12	8	49	54	61	82.5
F. W.	12	4	51	62.5	61.5	85
	12	8	52			
	13	3	52			
	13	11	51			
	16	11	52			
	18	2	52			
A. W.	13	2	53	48	63	82
W. U.	13		59			
	14	11	55	53	64.5	83.5
	16	3	53			
	19	2	53			
	24	11	55			
N. S.	14	3	41	45	58	85
	15	3	40			
	17	2	42			
	18	2	43			
	18	6	43			
L. R.	20	9	55	54	63.5	80.5
	21	9	56			
P. B.	7	6	50	48	68.5	75
D. S.	8	8	44	38	64	77
	9	7	44			
	10	1	46			
J. A.	10	8	59	53	65	80
J. L.	13	11	59	37	68	75
J. G.	14	9	60	45	64.5	79.5
	17	8	64			
	18	5	66			
J. M.	14	5	66	60	65	84
B. G.	15	2	64	55	60.5	85.5
R. M.	16	9	56	47	66	76.5
H. K.	17	4	54	53	65	82
	20		57			
E. C.	17	2	53	57	66.5	81.5
	19	7	54			
J. B.	19	11	69	38	80	70.5

*These measurements were made with correctional scales.

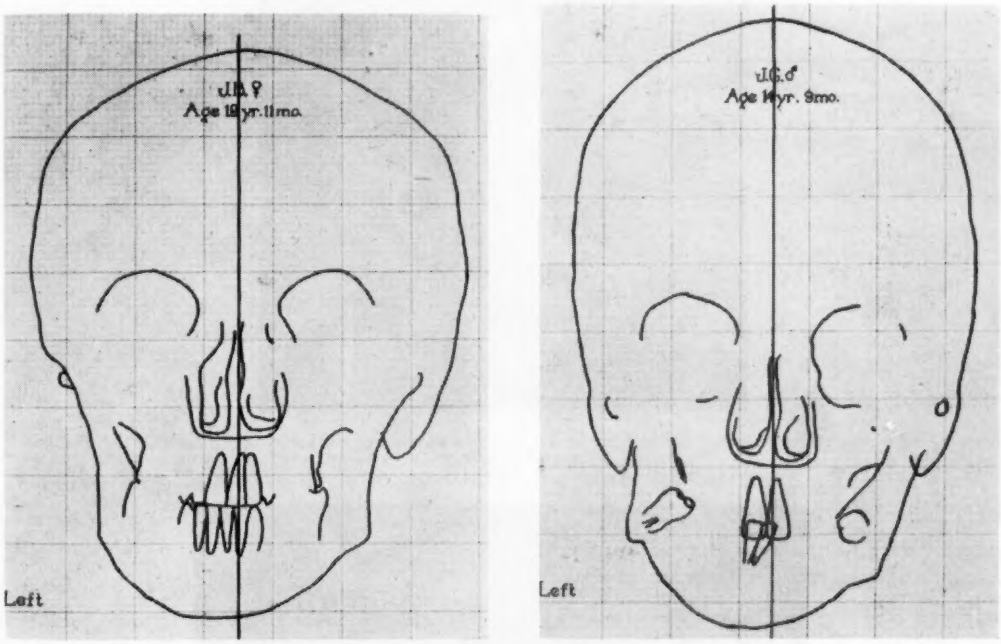
†The angle of the affected side was measured in the cases of unilateral arrest . The mean between the two mandibles was utilized where there was bilateral involvement.

revealed notching of the lower border. The patient was frequently unable to deviate the jaw toward the normal side and the mandibular midline shifted toward the abnormal side on protrusion.

With bilateral arrest there was usually a symmetrical type of deformity (Fig. 5). This resulted in a *Vogelgesicht* with a markedly retruded mandible and with the chin lying in the hyoid region. Lateral function was not always possible. Antegonial notching was present bilaterally in these cases.

ROENTGENOLOGIC FINDINGS

Cases Exhibiting Unilateral Arrests (Figs. 6, 7, 8, and 9, Table I).—Comparison of the roentgenograms of J. G. with the history of arrest at 2½ years with those of J. B. with an arrest occurring between 15 to 17 years illustrates two extremes of disturbed growth (Figs. 6 and 7). In the latter instance the mandibular midline deviated to the affected side and there was a slight asymmetry in mandibular form. The S. N.-lower border angle was 38 degrees. There was a Class I occlusal relation. In the case of the early arrest there was a marked skewing of the mandible toward the involved side. (In some instances this resulted in complete lingual occlusion of the mandibular teeth on the unaffected side.) The ramus was short and the



Figs. 6 and 7.—Tracings of frontal roentgenograms of two cases, J. B. and J. G., superposed on ruled paper to indicate the relative distorting effect of late and early condylar arrests respectively. The left side was involved in both cases. (See Table I for history.)

body height was reduced. The lower border of the mandible just anterior to the junction of the ramus and body was notched and presented an abnormal convexity which was readily palpated. Superposition of the mandibular tracings of the retarded side (Fig. 10) showed continued adherence to a distorted mode of growth over a period of four years. The S. N.-lower border angle was 45 degrees, indicative of a failure of downward development.

The patient (J. G.) had a Class II malocclusion. (In the orthodontic treatment of this case the upper first bicuspids were extracted and the anterior teeth were retracted. Although there was some improvement in appearance the result was far from satisfactory.)

Arthroplasty in this patient, as in others seen by us, did not restore the growth potential although there was improved function.

Cases Exhibiting Bilateral Arrests.—Roentgenographic examination of those patients having a bilateral arrest (Figs. 11 and 12, Table I) usually showed a symmetrical dysplasia.

Fig. 8.—Anteroposterior roentgenogram of D. S. showing characteristics of a unilateral condylar arrest. The right side was involved.

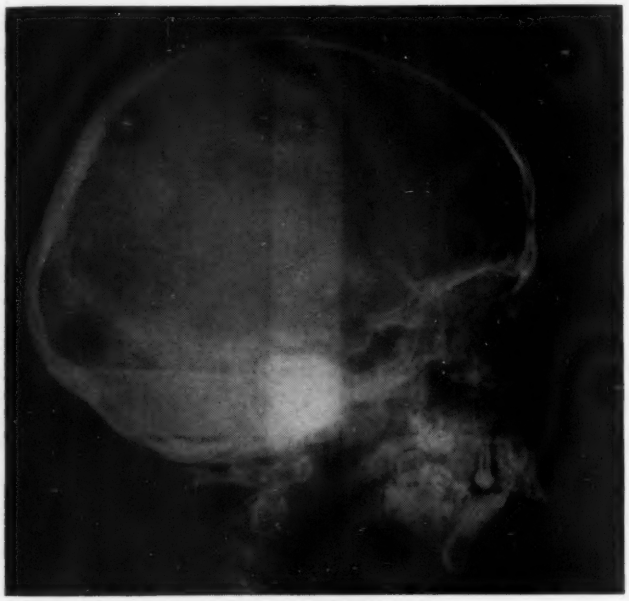


Fig. 9.—Lateral roentgenogram of D. S. Note notching of the right mandibular border.

Because of the failure in mandibular growth, there is an elimination of the downward and forward movement which is typical of normal development. Apparently the downward component is disturbed more profoundly than the forward component. The evidence for this lies in the findings that the angle which may be constructed between the anterior cranial base S. N. and the lower border of the mandible Go. Gn. invariably lies outside the normal range (32°± 4.9°). Angles N. S. Gn. and S. N. Gn. also deviate markedly from the normal (Fig. 13, Table II).

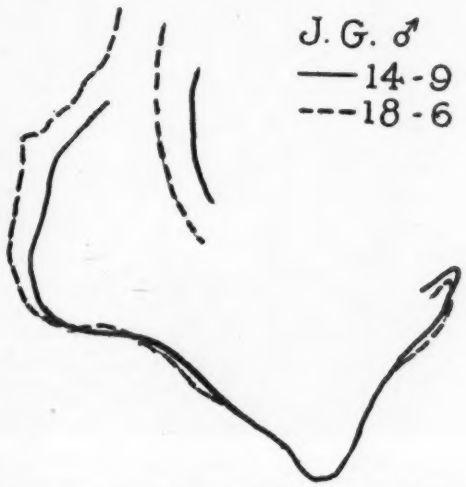


Fig. 10.—Superposed serial tracings of the left side of the mandible of J. G. The growth pattern adheres to its dysplastic form.

Excellent serial data were available for three of the cases (W. U., F. W., N. S., Figs. 14, 15, and 16.) The increment curves of the lower border of the mandible (Go. Gn.) for the period of observation were plotted and compared to a control curve. In all instances there was considerable underdevelopment and a more rapid approach to asymptotic form than in the normal, indicating a feeble growth potential which was never restored to healthy vigor. The dysplastic pattern was maintained and was unmodified by orthodontic treatment, which was generally not successful. Certainly growth of the bone was not stimulated and the facial disharmony was accentuated by the opening of the bite which usually resulted from such treatment.

The case W. U. (Fig. 16) of this group is particularly interesting. Change in mandibular form was observed here and first reported by Brodie[5] in 1941. The change to a dysplastic pattern ocurred following bilateral condylar resection. The new form had then remained unaltered for ten years. The change in the growth curve was in reality not a measure of length change here but rather a reflection of the profound modification of mandibular form. Thus the mandible was actually not shortened but the location of the Go. Gn. points had shifted.

Two of our eight cases of bilateral mandibular deformity developed as a result of polyarthritis in which the temporomandibular joint was also involved (J. F., A. G., Figs. 5 and 11). They presented a picture which did not vary essentially from the characteristic bilateral condylar growth arrest.

Fig. 11.—Lateral roentgenogram of J. F. showing the characteristics observed in a bilateral condylar arrest. This was associated with a generalized arthritis.

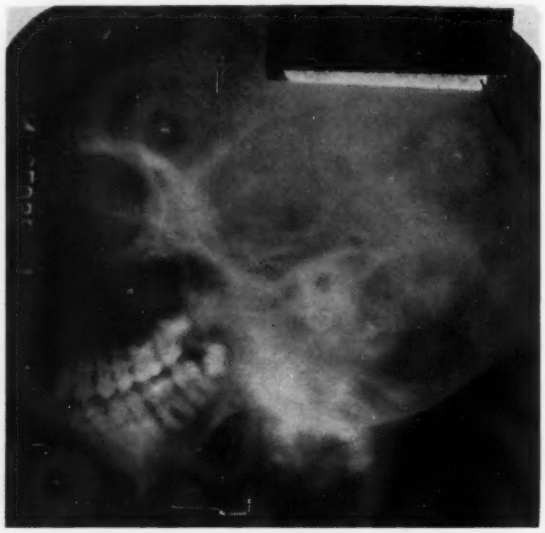


Fig. 12.—Laminagraph of right temporomandibular joint of A. G. (generalized arthritis). The condyle is flattened and shortened, characteristic of an arthritic process.

DISCUSSION

Disturbance of Growth.—The problem of growth retardation resulting from a noxious influence on epiphyseal cartilage was reviewed by Kuhns and

Swaim in a paper on arthritis in children.[12] They cited the work of Vogt (1876) and Harris (1930) who pointed out that inflammatory processes or circulatory disturbances in proximity to an epiphysis may lead to disturbances in growth. The present paper deals with the effect of such influences on the active cartilage center at the head of the mandibular condyle. The cases reported illustrate strikingly the typical jaw deformity which results from the ensuing arrest.

When a premature ossification of epiphyseal cartilage occurs, as in chronic arthritis in children, subsequent growth expectancy is poor. It appears that scarring and early ossification of the condyle head may occur not only in polyarthritis but following trauma or infection.

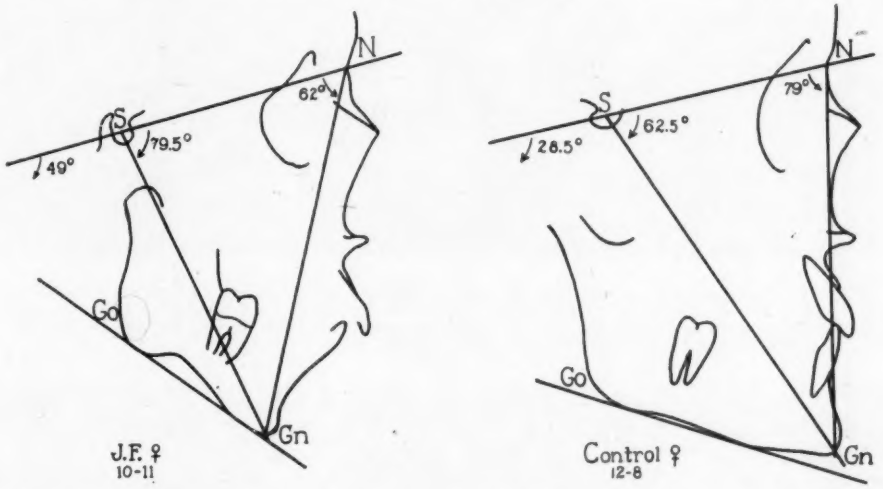


Fig. 13.—Tracings of facial patterns showing the differences in three significant angles noted between a normal child and one exhibiting a bilateral condylar arrest. The normal range is indicated in Table II.

The severity of the deformity is related to the chronology and duration of the arrest. In the case of a unilateral arrest, an early disturbance leads to a marked facial asymmetry. Involvement in the period of growth regression leads to more subtle disturbances which may be reflected primarily by dental occlusal changes such as a shift in the mandibular midline without any profound change in mandibular size or form. This accounts for difference in the degree of distortion noted between J. G. and J. B. Similarly the earlier bilateral arrests are associated with more pronounced deformities.

Sometimes the arrest is succeeded by a period of growth which is, however, considerably decelerated. It is important to know something about the growth potentialities in these cases particularly where there is an ankylosis of the jaw. This may be deduced only from serial records over a period of two or three years. If the serial study indicates that growth activity is continuing, even at a low rate, surgical intervention should be ruled out because such intervention will only superimpose another severe growth arrest as in the case of W. U. If the cartilage has been prematurely ossified or

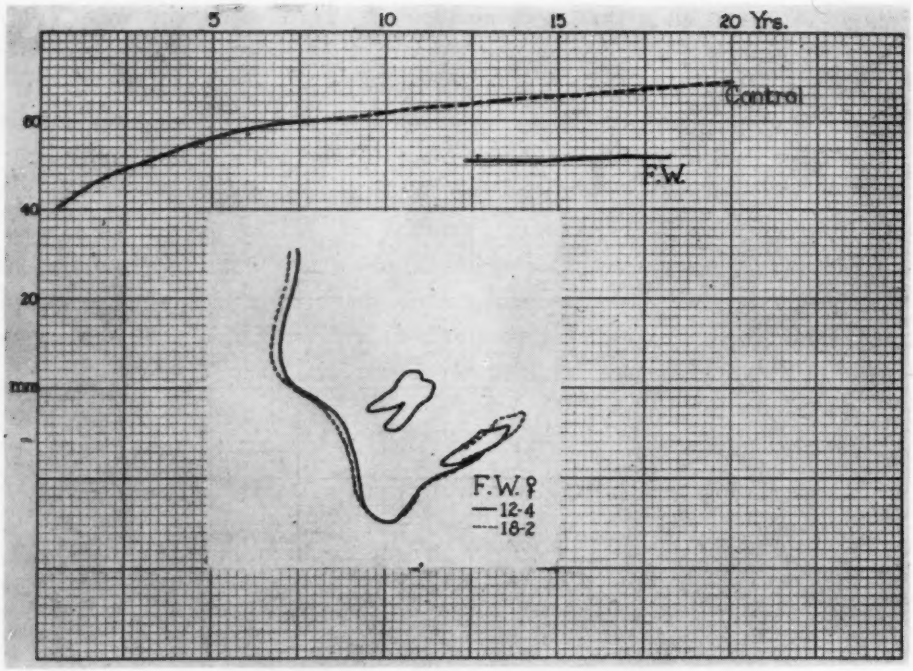


Fig. 14.—Tracings of mandible of F. W. Increment curve of lower border length (Go.-Gn.) from 12 years 4 months to 18 years 2 months is plotted. A control curve has been developed from Brodie's measurements.[4] This has been extrapolated beyond the 8 year level. (Limited unpublished data tend to confirm the validity of the extrapolation.)

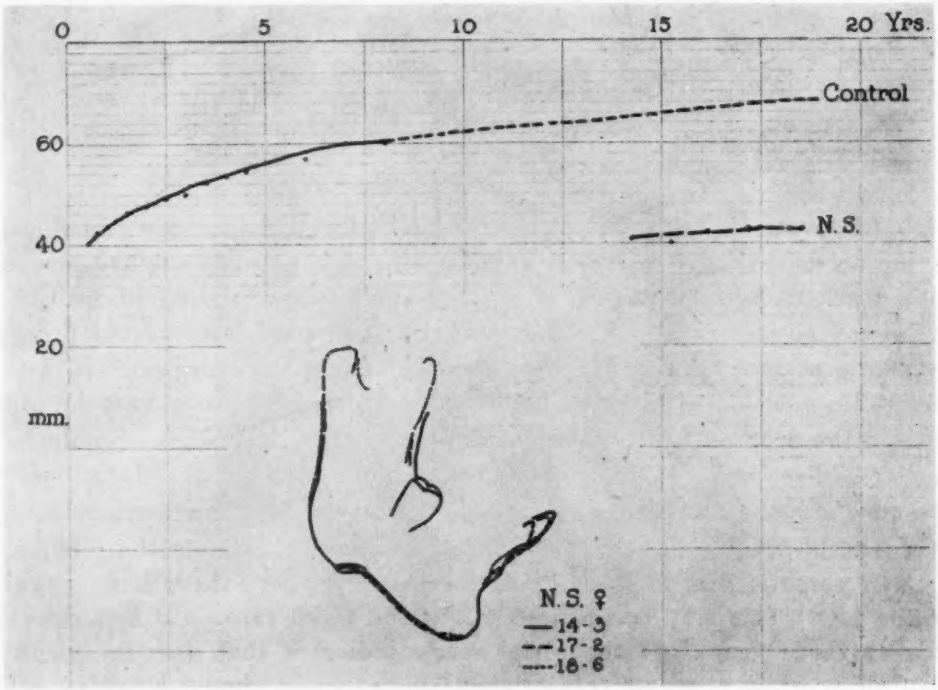


Fig. 15.—Tracings of mandible of N. S. Increment curve of lower border length (Go.-Gn.) from 14 years 3 months to 18 years 6 months is plotted.

so badly scarred as to preclude further growth, surgery is not contraindicated from the growth standpoint. In older individuals this does not constitute a problem.

The facial pattern in these cases of arrest lies outside the normal range (Fig. 13); the deviation is uniform and characteristic and seems to be entirely a result of the mandibular deformity. The failure in forward development accounts for the acute angle S. N. Gn. and the more obtuse N. S. Gn. Failure in ramus height growth is reflected in the larger than normal S. N.-mandibular border angle. This type of facial pattern is also seen in some extreme types of malocclusion (marked Class II Division I malocclusions). It is entirely possible that the etiology of such conditions may be traced to growth disturbances in the condylar center.

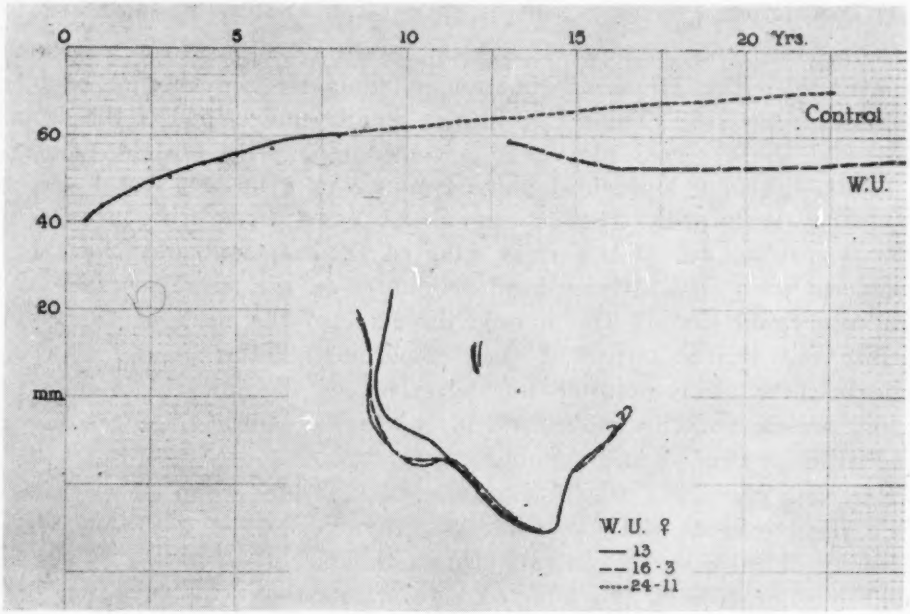


Fig. 16.—Tracings of mandible of W. U. Increment curve of lower border length (Go.-Gn.) from 13 years to 24 years 11 months is plotted.

One may speculate upon the reason for the notching at the antegonion and the apparent distortion in mandibular form which are pathognomonic of the condylar growth arrest. The most satisfactory explanation would appear to be that growth continues at the angle of the mandible as a result of subperiosteal apposition. Because of the failure at the condyle, forward and downward movement of the body does not occur; there is then a localized thickening of the bone at the angle which accentuates the antegonion. This, coupled with the obtuse angle formed between the cranial base and the lower border of the mandible, is responsible for the characteristic "warping."

Muscle imbalances have been regarded by some as the major factors involved in producing the dysplasia. The validity of such an assumption is difficult to sustain in view of the following findings:

1. Resections either of the condyle or horizontally through the superior portion of the ramus for the correction of mandibular prognathism were performed on an older group of patients (17 to 35 years of age). In none of these cases has there been any significant change in the form of body of the mandible over a subsequent period of several years.

2. Injury to the condylar area in the cases reported here was not always associated with muscle disturbance as evidenced by the normal range of functional movements in some.

3. The authors have seen cases of functional limitation of obscure etiology, that is, almost complete inability to open the mouth, where the condylar area was apparently undisturbed. In these individuals there was no deformity of the jaw.

4. This deformity does not occur in adult temporomandibular ankylosis.

Disturbance of Function.—Condylar growth disturbances are frequently associated with limitations of function, particularly the absence of lateral excursion on one side (Table I). This is readily understood if the dynamic anatomy of the external pterygoid is considered. This muscle, which has two heads, lies in a horizontal plane running in a posterolateral direction from before backward. The superior head passes from the inferior part of the lateral surface of the great wing of the sphenoid and from the infratemporal crest; the inferior head originates on the lateral surface of the lateral pterygoid plate. The muscle inserts into the neck of the condyle and into the articular disc of the temporomandibular joint. The right muscle is therefore responsible for movement of the jaw to the left while the left muscle controls movement to the right. Both sides act together in executing protrusive and opening movements.

External pterygoid function was tested in our group of patients by having them execute these movements. Involvement of a muscle was indicated by (1) absence of contralateral excursion, (2) deviation of the mandibular midline toward the affected side on opening, (3) deviation of the midline toward the affected side on protrusion.

There is some evidence to indicate that the suprahyoids take over the major role of depressors of the mandible when both external pterygoids are inactivated.[18]

TREATMENT

The problem of treatment is a difficult one. There is no mechanism that will compensate for the lost or retarded growth. Although the deformity may not be progressive, except in some cases of unilateral arrest, it is not self-correcting; the dysplastic pattern of growth continues.

Since orthodontic treatment is capable only of modifying the alveolar process it is not effective in correcting the basic deformity. The orthodontist can only strive for a correction of the occlusal relations of the teeth. Even this is difficult because of the growth lag. It has been pointed out[20] that the prognosis for successful orthodontic treatment of patients with facial patterns similar to those included here is poor. The reason may be similar.

In most of our cases the mandibular dental arch was badly crowded and the upper incisors markedly protrusive. In order to secure the retraction of the upper incisors, the proper alignment of the mandibular teeth, and a functional locking of occlusal planes, compromise treatment involving judicious extraction of some units should be considered.

The collaborative efforts of the plastic surgeon and the orthodontist are necessary to attain cosmetic improvement. The insertion of autogenous cartilage transplants on the flattened side of the face in the asymmetries and in the mental area where there has been a bilateral arrest are particularly effective. Attempts to bring the mandible forward by a combination of surgical and orthodontic means have not met with consistent or noteworthy success to date.

CONCLUSIONS

1. The condylar area is characterized by intense chondral activity and subsequent ossification similar to that occurring in the epiphysis of a long bone. This activity is greatest during the fetal period and the early years, tapering to a standstill between the ages of 16 and 20 years.

2. Injury to the condylar center results in a growth arrest and consequent characteristic distortion of mandibular form.

3. Because of its condylar insertions the functions of the external pterygoid muscle are frequently impaired in such cases.

4. The mandible that has become dysplastic through an early arrest will, if recovery occurs, follow the dysplastic pattern without any compensating acceleration, thus the end result is an underdeveloped mandible.

5. The growth disturbance resulting from the arrest is not corrected either by orthodontic treatment or by surgical procedures. However, these measures may yield a degree of cosmetic improvement.

6. Surgical interference in the temporomandibular joint area should be undertaken most cautiously and only after serial observation of the patient has shown that growth has ceased. Otherwise, there is danger that an additional arrest will be superimposed on an already retarded growth center.

We wish to express our appreciation to Dr. John Thompson and to Dr. Harold Noyes who made material available from their files.

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ZIPPERED ELASTIC STOCKINGS

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(From the Thomas-Davis Clinic)

THE use of elastic stockings for the treatment of venous passive congestion and its complications (phlebitis, ulcers, and eczema of varicosities) of the lower extremities is a generally accepted and valuable procedure.

With the aforementioned complications the application of an elastic stocking is painful, often causing loss of newly hard-won epithelium in eczematoid or nearly healed ulcerations.

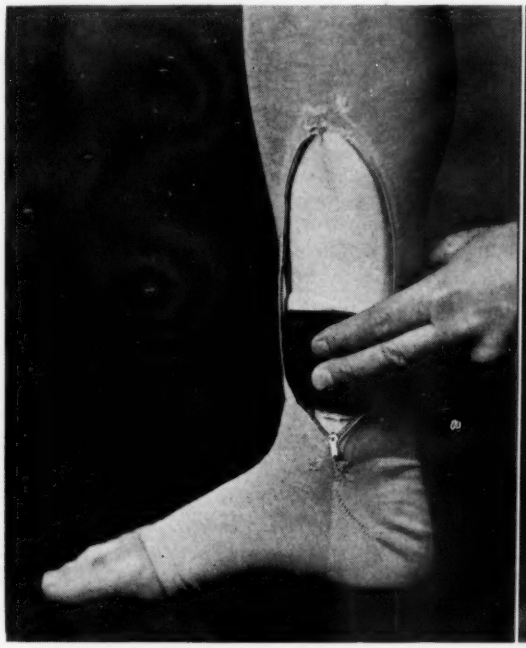

Fig. 1.

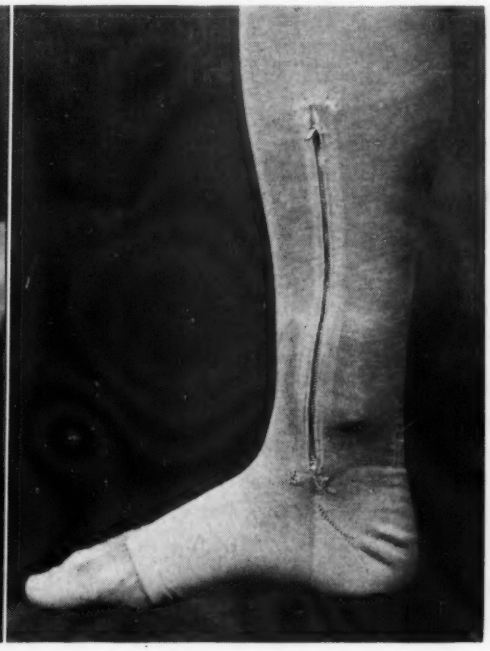

Fig. 2.

Fig. 1.—Application of gauze dressing at the site of a varicose ulcer. Overlying the gauze is a rubber sponge holding the dressing in place, eliminating need for adhesive tape. This sponge also gives local pressure over the ulcer, accelerating healing.

Fig. 2.—Zipper closed, holding dressings in place. Muscular activity does not dislodge dressing.

By incorporating a zipper as illustrated, the difficulty and pain in pulling on the elastic support are obviated. When applying dressings over a granulating area it has been found especially advantageous to use a zippered stocking as no adhesive tape is necessary, avoiding adhesive tape irritation, and dressings may be easily changed (Figs. 1 and 2).

The simplicity of sewing a zipper in place is demonstrated by the fact that in all instances the patient or a member of his family has sewn the zipper in the stockings.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

III. POST-TRAUMATIC RENAL INSUFFICIENCY

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INTRODUCTION

THE importance and frequent occurrence of renal failure in that relatively small group of battle casualties who are seriously wounded must be emphasized. The present report describes: (1) the clinical, physiologic and biochemical features of this syndrome, as we observed it; and (2) the forms of treatment that were employed including certain therapeutic errors.

METHODS OF STUDY AND DIVISION OF CASES

Three main criteria have been utilized in grouping the patients who developed this complication: (1) The "high azotemia" group includes every patient who, at some time during the period we observed him, had a nonprotein nitrogen level of 65 mg. per cent or more. (2) The oliguria group includes patients with urinary output of 100 to 600 c.c. for at least one twenty-four hour period. (3) The anuria group represents those patients with less than 100 c.c. of urinary output for at least one twenty-four hour period.

Most of the cases in the "high azotemia" group are also included in either the oliguria or the anuria group (Table I). A large proportion of the cases in the oliguria and anuria groups fall, of course, into the "high azotemia" (Table II).

There is much overlapping in the three groups. Most of the averages, however, were obtained from the "high azotemia" group, or portions thereof. Analysis of the anuria and oliguria groups in separate categories seemed desirable because a low urinary output provides a simple and useful means of recognizing such cases clinically.

Clinical Features

Mortality.—The importance of uremia as a primary cause of death in all three groups is demonstrated in Table III. The cause of death was assigned

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TABLE I. TYPES OF URINARY OUTPUT IN THE "HIGH AZOTEMIA" GROUP

TYPES	NUMBER
Normal output	10
Oliguria	29
Anuria	27
Output unknown	7
Total cases	73

by clinical evaluation, blood chemistry, and autopsy findings. Four of the five patients classified as "no uremia" or "unknown," in the anuria group, died probably with at least coincident uremia. From these figures it is obvious that any patient who develops anuria, by our definition, has an extremely grave prognosis (30 patients, 91 per cent mortality in our series, and 22 patients, 67 per cent in uremia). In the oliguria group, while the mortality was high (21 patients, 47 per cent in the whole group) only 12 patients, or 27 per cent, died in uremia. In the "high azotemia" group, 50 patients, or 69 per cent, died and 34 patients, or 47 per cent, were in uremia.

TABLE II. INCIDENCE OF "HIGH AZOTEMIA" IN THE ANURIA AND OLIGURIA GROUPS

	ANURIA	OLIGURIA
"High azotemia"	27	29
No azotemia	1	16
Nonprotein nitrogen unknown	5	0
Total cases	33	45

Degree of Initial Shock.—Table III also shows the relationship between degree of initial shock and subsequent renal failure. If one excludes the crush cases, a true transfusion incompatibility, and a case of sulfathiazole crystalluria in the no-shock group, it becomes evident that there is a definite preponderance of renal failure in those who were recognized as having severe or moderate initial shock. Thus, if the exclusions mentioned are made, 86 per cent of the azotemia group, 73 per cent of the oliguria group, and 76 per cent of the anuria group had moderate or severe initial shock. Many patients may have had transient shock, even of several hours' duration, before hospital entry but with no sign of

TABLE III. TYPES OF DEATH AND DEGREE OF INITIAL SHOCK IN "HIGH AZOTEMIA," OLIGURIA, AND ANURIA

GROUP	TOTAL	LIVED	DIED	TYPES OF DEATH				DEGREE OF INITIAL SHOCK					
				UREMIA	UREMIA CONTRIBUTORY	UREMIA COINCIDENT	NO UREMIA, OR UNKNOWN	TOTAL	NONE	SLIGHT	MODERATE	SEVERE	UNKNOWN
"High azotemia"	73	23	50	34	3	13	0	73	6*	6	27	33	1
Oliguria	45	24	21	12	1	5	3	45	3	8	13	20	1
Anuria	33	3	30	22	1	2	5	33	8†	3	6	16	0

*Includes two crush cases, one transfusion incompatibility, and one case with slight postoperative shock.
†Includes one sulfathiazole crystalluria, one transfusion incompatibility, and two crush cases.

this on entry. Our recorded figures are doubtless too low. However, it is not clear that the severity of the renal lesion is entirely determined by the degree of shock. Our series includes a few patients who, so far as we could determine, never had any marked degree of shock and yet developed subsequent renal insufficiency (Cases 22, 120, 138).[1]

Role of Uremia as a Cause of Death, and Its Relationship to Time of Death After Wounding.—The time of death after wounding in 51 patients with renal insufficiency is shown in Table IV. Of those in whom uremia was the primary cause of death, 41 per cent died in the first five days, 50 per cent in the second five days, or 91 per cent within ten days after wounding. Likewise, of all the patients, 94 per cent died within the first ten days. The significance of this time factor should be emphasized, for evidence will be presented that if the patients can be carried through this critical ten-day period, they stand a fair chance of recovery.

TABLE IV

TIME OF DEATH AFTER WOUNDING (DAYS)	ROLE OF UREMIA IN CAUSE OF DEATH (NUMBERS OF CASES)			
	PRIMARY	CONTRIBUTORY	COINCIDENT	UNKNOWN
1 to 5	14	2	8	3
6 to 10	17	1	3	0
11 to 14	3	0	0	0
Totals	34	3	11	3

Types of Wounds.—Types of wounds in the three groups of renal insufficiency are shown in Table V. In the "high azotemia" group, peripheral wounds with fracture, and intra-abdominal wounds are of equal frequency. In the oliguria group, peripheral wounds predominate; whereas in the anuria group, intra-abdominal wounds are somewhat more frequent. Thoracic wounds rank third in all three groups. Wounds of the liver, kidneys, and urinary tract occurred, but not in high percentage in any group.

TABLE V. TYPES OF WOUNDS OR INJURIES IN PATIENTS WITH "HIGH AZOTEMIA" OLIGURIA, AND ANURIA

TYPE OF WOUND	"HIGH AZOTEMIA" (NO. OF CASES)	OLIGURIA (NO. OF CASES)	ANURIA (NO. OF CASES)
Multiple major wounds	21	10	7
Single major wound	52	35	26
Peripheral *with* fracture	32	18	11
Intra-abdominal	32	14	13
Thoracic	15	10	7
Peripheral *without* fracture	8	5	5
Thoracoabdominal	6	7	4
Liver	12	7	8
Kidney	10	7	6
Nephrectomy	6	4	4
Urinary tract, other than kidney	6	3	4
Crush cases	4	1	4
Burn	1	1	0
Spinal cord injury	2	1	0
Sulfathiazole crystalluria	0	0	1
Incompatible blood transfusion	1	0	1
Total cases included	73	45	33

Incidence of Hypertension, Edema, Eye Ground Change.—Table VI indicates the number of patients in the "high azotemia" group who at some time in their course had a systolic blood pressure of 135 mm. of mercury or higher, or a diastolic of 90 mm. or higher. These levels were decided upon as the probable upper limits of normal for the age group into which our patients fell. The hypertension was first recorded in the majority of patients within the first seven days after wounding, injury, or crush. In only 4 of the 71 were initial recordings made after that time. The probability is that even these patients had an unobserved hypertension prior to the first determination recorded. In general, the pressure rose gradually, reaching a maximum between the third and sixth days after wounding. This agrees essentially with the time of maximum nitrogen retention in the blood.

TABLE VI. INCIDENCE OF HYPERTENSION IN "HIGH AZOTEMIA"

	TOTAL	HYPERTENSION (NO. CASES)	NO HYPERTENSION (NO. CASES)	HYPERTENSION (PER CENT)
Lived	22	15	7	68
Lived, with minimal renal failure	12	5	7	42
Lived, with recovery diuresis	10	10	0	100
Died	49	29	20	59
Died, uremia primary cause	34	27	7	79
Died, uremia contributory	3	1	2	33
Died, uremia coincident	12	1	11	8
All cases	71*	44	27	62

*All cases are included in which adequate record of blood pressure was kept.

Of the 20 patients who died but did not develop hypertension, 13 died within the first four days after wounding, 3 within six days, and 4 within six to ten days. Many of these never really recovered from shock. Most of them possibly would have developed hypertension if they had lived longer, especially the 7 patients in whom the primary cause of death was uremia.

Edema was clinically observed in 23 of the 73 cases in the "high azotemia" group. The degree varied, but when present was usually generalized, involving all extremities and the face. Eighteen instances were in patients who died. Three patients had generalized convulsions. Eye grounds were examined in 7 cases; 3 showed abnormalities—flame-shaped hemorrhages in 2, and a small exudate in 1. A pericardial friction rub was heard in one patient who died in uremia; he showed pericarditis at necropsy.

LABORATORY METHODS

The laboratory methods are described in detail elsewhere.[1]

BIOCHEMICAL ABNORMALITIES OF THE BLOOD AND URINE

In studying these patients who developed renal insufficiency, we were dealing with a unique group of individuals. They were all normal men in a young age group and prior to wounding, so far as known, were physiologically sound. They had sustained severe wounds which almost at once produced changes in

their internal environment.[1, 2] The wounds and the changes produced were not severe enough, considering the present effectiveness of resuscitation and other early treatment, to cause early death. Largely because they were adequately treated preoperatively, they withstood operation fairly well; but beginning with the first day or two postoperatively (or after trauma, if no surgery was done), they began to show clinical and laboratory evidence of inadequate renal function. The renal failure progressed rapidly, and in most instances the patients either died in uremia within the first ten days or later showed signs of beginning improvement of renal function (as shown by diuresis and clearance of nonprotein nitrogen) and subsequently recovered.

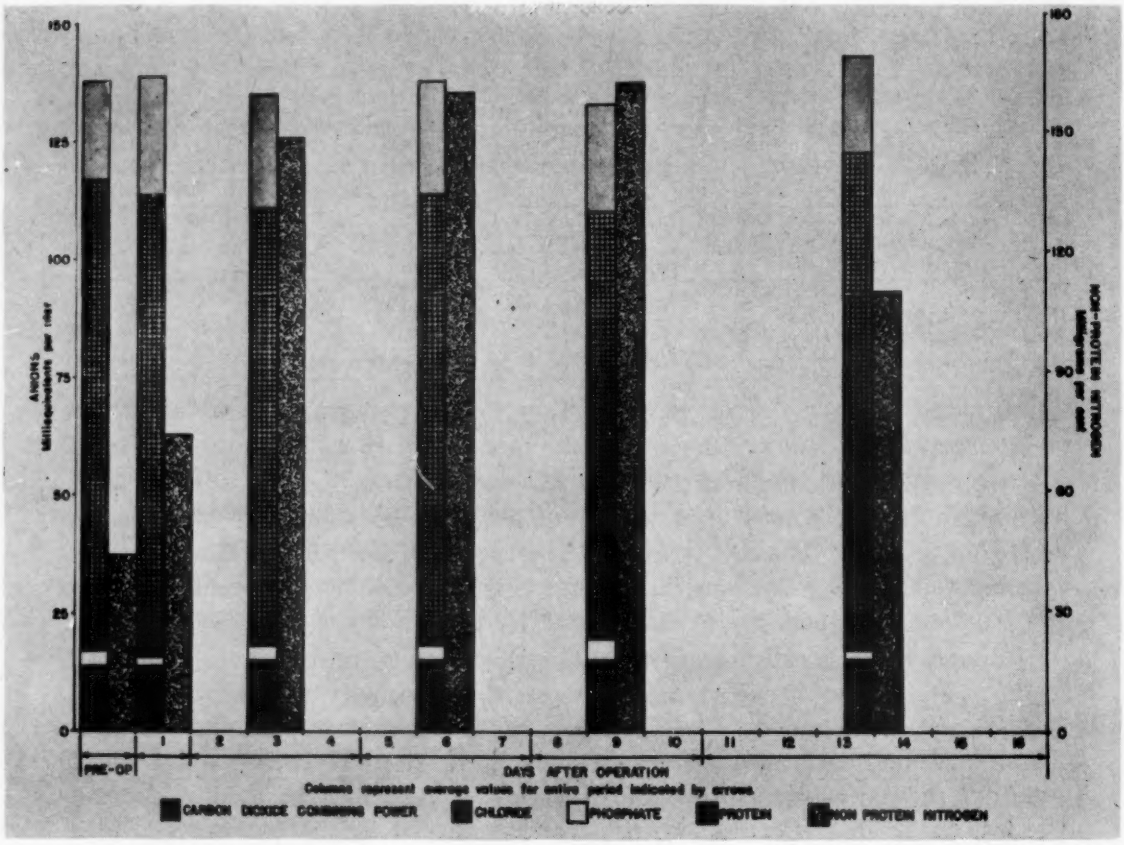

Fig. 1.—Plasma anions and nonprotein nitrogen, average values for all cases in azotemia group.

In presenting the large number of blood chemistry and urine determinations carried out in these patients, an attempt has been made to group them in such a way that the averages represent as far as possible the typical physiologic and biochemical alterations which take place during the acute period up to the time of death, or, in those who lived, through the recovery phase as long as we could follow them. Variations from this typical picture in individual cases will also be mentioned where these seem important. For complete records, the reader is referred to the clinical case histories.[1]

TABLE VII. AVERAGE PLASMA NONPROTEIN NITROGEN, AND PLASMA OR SERUM PROTEINS AND ELECTROLYTES IN PATIENTS WITH "HIGH AZOTEMIA"*

	PREOPERATIVE	POSTOPERATIVE DAYS				
		1	2 TO 4	5 TO 7	8 TO 10	11 TO 16
Plasma N.P.N. (milligrams per cent)	47.3 ± 4.8 (21 cases)	72.8 ± 4.2 (31 cases)	143.1 ± 9.3 (54 cases)	182.2 ± 17.2 (29 cases)	175.8 ± 29.8 (13 cases)	127.6 ± 23.4 (10 cases)
Plasma carbon-dioxide combining power (milliequivalents per liter)	21.8 ± 1.3 (21 cases)	24.9 ± 1.3 (20 cases)	25.6 ± 0.9 (47 cases)	23.6 ± 1.5 (23 cases)	21.4 ± 2.1 (11 cases)	19.5 ± 1.5 (8 cases)
Plasma chloride (milliequivalents per liter)	98.8 ± 0.8 (21 cases)	96.8 ± 0.9 (31 cases)	93.7 ± 1.6 (54 cases)	93.1 ± 3.0 (28 cases)	91.8 ± 6.3 (13 cases)	103.0 ± 5.3 (10 cases)
Plasma phosphate (milliequivalents per liter)	3.9 ± 0.3 (18 cases)	2.6 ± 0.2 (26 cases)	3.7 ± 0.3 (45 cases)	3.7 ± 0.3 (26 cases)	4.7 ± 0.5 (9 cases)	3.3 ± 0.3 (10 cases)
Plasma protein (milliequivalents per liter)	14.8 ± 0.1 (21 cases)	15.1 ± 0.1 (32 cases)	15.6 ± 0.1 (53 cases)	15.8 ± 0.2 (31 cases)	15.8 ± 0.3 (13 cases)	15.8 ± 0.3 (10 cases)
Serum sodium (milliequivalents per liter)	146.3 ± 3.7 (5 cases)	147.5 ± 3.7 (6 cases)	141.3 ± 2.5 (21 cases)	137.8 ± 5.1 (8 cases)	140.7 ± 4.4 (6 cases)	151.7 ± 5.7 (7 cases)
Plasma magnesium (milliequivalents per liter)	2.0 ± 0.1 (13 cases)	1.4 ± 0.1 (5 cases)	2.4 ± 0.3 (13 cases)	2.8 ± 0.6 (9 cases)	3.3 (3 cases)	2.2 ± 0.3 (5 cases)

*The averages were obtained from determinations done on 73 patients with an N. P. N. level of 65 mg. per cent or over at some time during their course. Where more than one determination was done on a given patient, during a postoperative group of days, only one (the most abnormal value) was included in the averages. Standard errors of the mean are shown. N. P. N. represents nonprotein nitrogen.

Nitrogenous Waste Products and Phosphorus

Nonprotein Nitrogen.—Fig. 1 is constructed from Table VII, which represents average values in "high azotemia" cases. Although the variation is rather wide in some groups, an adequate number of cases probably is included

TABLE VIII. AVERAGE PLASMA NITROGENOUS WASTE PRODUCTS AND PHOSPHORUS IN PATIENTS DYING IN UREMIA (MILLIGRAMS PER CENT)

DAYS AFTER WOUNDING	NONPROTEIN NITROGEN	CREATININE	URIC ACID	PHOSPHORUS
1	69 ± 10.3 (9 cases)	3.0 ± 0.24 (9 cases)	4.1 (3 cases)	4.2 ± 0.47 (8 cases)
2	118 ± 11.5 (13 cases)	4.8 ± 0.24 (13 cases)	7.3 ± 1.1 (5 cases)	4.1 ± 0.28 (12 cases)
3	132 ± 6.2 (16 cases)	6.3 ± 0.26 (16 cases)	12.8 ± 2.4 (8 cases)	5.8 ± 0.42 (14 cases)
4	178 ± 5.1 (16 cases)	8.1 ± 0.47 (16 cases)	12.9 (3 cases)	5.9 ± 0.36 (14 cases)
5	245 ± 18.9 (13 cases)	8.9 ± 0.53 (13 cases)	15.0 (3 cases)	7.1 ± 0.96 (12 cases)
6	253 ± 13.0 (8 cases)	9.5 ± 0.70 (9 cases)	18.4 (3 cases)	6.9 ± 0.22 (8 cases)
7	234 ± 26.3 (4 cases)	7.8 ± 1.83 (4 cases)	---	6.6 (3 cases)
8	255 (2 cases)	11.3 (2 cases)	---	7.1 (2 cases)
9	278 ± 16.0 (5 cases)	11.4 ± 0.44 (5 cases)	---	6.8 (3 cases)
10	314 (3 cases)	11.4 (3 cases)	---	7.7 (3 cases)
11	296 (2 cases)	10.3 (2 cases)	---	6.8 (2 cases)

to give a fairly representative picture during the periods shown. In general, nitrogen retention is already significant by the first postoperative day, increases rapidly during the first ten days, and then begins to decline.

As shown previously, most of the patients who die do so in the first ten days; therefore, the fall in the tenth to fifteenth days chiefly represents patients who recovered. In general, the nonprotein nitrogen level rose progressively to the day of death in those patients who died primarily of renal insufficiency (Table VIII, Fig. 2). However, two patients (Cases 66 and 93)[1] who

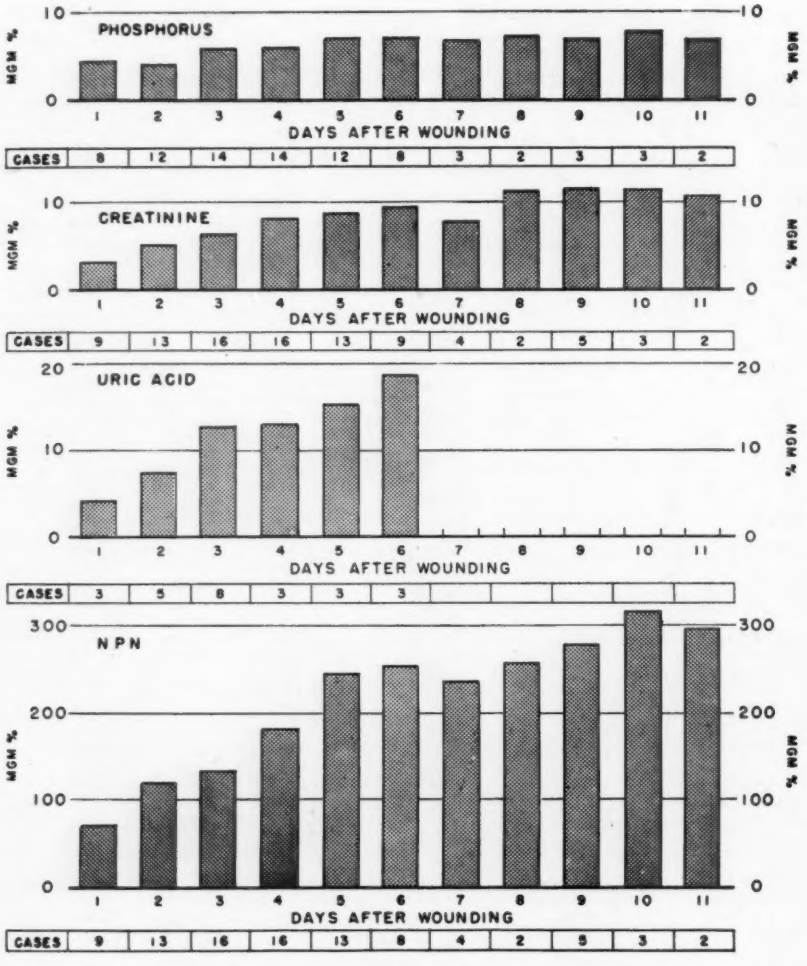
PHOSPHORUS
CREATININE
URIC ACID
NPN
MGM %
% MGM
DAYS AFTER WOUNDING
CASES
8 12 14 14 12 8 3 2 3 3 2
9 13 16 16 13 9 4 2 5 3 2
3 5 8 3 3 3
9 13 16 16 13 8 4 2 5 3 2

Fig. 2.—Average plasma nitrogenous waste products and phosphorus in patients dying in uremia (milligrams per cent).

lived longer than ten days after wounding fourteen and thirteen days, respectively) began to show some evidence of returning renal function. The significance of this fact in relation to therapy cannot be too strongly emphasized: it is important to avoid any measure which might precipitate death before this natural recovery can occur.

An attempt was made to determine whether the development of azotemia could be correlated with the degree of initial shock, but this was not successful.

As mentioned previously, in the total number of patients who developed post-traumatic azotemia, oliguria, or anuria, a large proportion had severe or moderate initial shock. A few patients developed renal insufficiency after slight shock or no shock (so far as we could determine), and the subsequent renal failure was as severe in these patients as in those with previous shock.

Similarly, there is no evidence that nonprotein nitrogen is initially higher in patients who subsequently die of uremia, or develop oliguria or anuria, than in those who develop less severe renal failure.

Creatinine.—Roughly, the level of creatinine rose in the plasma as the total nonprotein nitrogen did (Fig. 2, Tables VII and VIII).

Urea.—Plasma urea nitrogen level was determined simultaneously with total nonprotein nitrogen in 15 cases (Table IX). Like creatinine, it rose approximately as the total nonprotein nitrogen rose. The relationships of these three substances when nonprotein nitrogen is elevated are shown in the table. The averages were obtained by using thirty-eight determinations from a larger series on 15 patients, but including only those in which nonprotein nitrogen was over 100 mg. per cent. If more than one determination was included from the same patient, the individual samples were drawn at least twenty-four hours apart.

TABLE IX

	PLASMA AVERAGES (MG. PER CENT)			RATIOS (AVERAGES)	
	NONPROTEIN NITROGEN	UREA NITROGEN	CREATININE	UREA / N.P.N.	CREATININE / N.P.N.
Elevated*	193 ± 12	137 ± 9	7.3 ± 0.47	0.71 ± 0.01	0.039 ± 0.001
Normal	35	18	1.0	0.51	0.028

*Thirty-eight determinations on fifteen patients.

Although all waste products which make up the total nonprotein nitrogen rose in our patients, these products did not accumulate in exactly the same proportions seen in the normal individual, if these figures represent a fair sample.

Excretion of Urea and Creatinine.—In 2 patients who died in the first five postoperative days twenty-four hour urea nitrogen and creatinine excretion were measured. Table X shows the relations of the total amounts of these substances in the urine to plasma levels, urine specific gravity, and urinary output.

The rising plasma level of nitrogenous waste products, accompanied by urinary excretion in low amount of these same substances, is distinctly shown. The falling output and low specific gravity of the urine are directly related to these changes.

Phosphorus.—The well-known retention of phosphorus in renal failure was present in our cases, and in general paralleled the degree of nitrogen retention (Fig. 2, Tables VII and VIII.) In these patients with post-traumatic azotemia, phosphorus retention is probably due primarily to impaired ability to excrete that substance; the hyperphosphatemia seen in patients in shock soon after wounding is due possibly to release of phosphates secondary to muscle damage.[1, 2]

Relationship Between Calcium and Phosphorus.—Twelve patients with azotemia had calcium and phosphorus determinations. The well-known recip-

TABLE X

	OUTPUT OF URINE (C.C.)	SPECIFIC GRAVITY OF URINE	N.P.N. (PLASMA) (MG. %)	UREA NITROGEN (URINE) (GM. PER 24 HR.)	CREATININE (PLASMA) (MG. %)	CREATININE (URINE) (GM. PER 24 HR.)
Case 108 (Patient died in uremia)						
Day of operation	100*	1.032*	37	0.13*	1.61	0.2*
First P.O. day	185	1.014	77	0.54	3.9	0.33
Second P.O. day	155	1.012	113		5.08	0.32
Third P.O. day	---		170		6.15	
Case 107 (Uremia a contributory cause of death)						
Preoperative†	60	1.028	27		1.11	
First P.O. day	1560	1.017	41	7.2	1.61	1.2
Second P.O. day	1570	1.019	46	9.4	1.64	1.32
Third P.O. day	1540	1.015	--	10.9		1.35
Fifth P.O. day	800	1.012	73	4.6	4.10	0.5
Sixth P.O. day			152		5.9	

*Urine specimen represents nineteen hours only.
†Specimens taken preoperatively on day of operation.

TABLE XI

CASE NUMBER	CALCIUM (MG. %)	PHOSPHORUS (MG. %)	N.P.N. (MG. %)	DAYS POST-OPERATIVE	OUTCOME
138	10.6	6.4	166	4	Recovery diuresis
	10.5	6.2	162	14	
133	9.4	4.7	108	10	Recovery diuresis
	9.5	5.4	101	14	
60	9.9	5.0	98	8	Recovery diuresis
93	9.0	6.0	155	5*	Death in uremia
	9.3	7.3	287	11*	
37	9.0	2.1	140	4	Recovery—never had oliguria
112	8.9	4.0	67	2	Recovered with minimal renal failure
108	8.6	5.1	77	1	Death in uremia
9	8.4	10.9	224	8†	Death in uremia
	7.6	12.6	201	9†	
123	8.0	4.3	120	3	Death in uremia
78	7.8	8.9	178	4*	Death in uremia
22	7.7	6.5	294	5	Death in uremia
25	7.4	5.3	166	2	Death in uremia
Averages for pts. with Ca 9 or over (8 determinations)	9.7	5.4	152		
Averages for pts. with Ca less than 9 (8 determinations)	8.1	7.2	166		

*Days after crush injury.
†Days after transfusion reaction.

rocal relationship between calcium and phosphorus is present in the majority of these cases (Table XI).

Uric Acid.—Uric acid, like phosphorus and creatinine, rose as the nonprotein nitrogen did, in patients who developed azotemia; the same proportion of uric acid to total nonprotein nitrogen was roughly maintained while the retention of both was progressing with renal failure (Fig. 2, Table VIII). The elevated uric acid seen soon after wounding, and possible mechanisms for it, have been discussed elsewhere.[1, 2]

Acid-Base Balance

Anions.—

Plasma carbon-dioxide combining power (and blood pH): The only group with a sufficient number of determinations for dependable averages was that of all the cases of "high azotemia" (Table VII). In these cases (Fig. 3) initial low values were demonstrable, followed by a rise toward normal on the first postoperative day. Throughout the next two weeks, there was a gradual fall. Inspection of individual cases showed certain qualitative trends.[1] Patients with azotemia who had the most nitrogen retention, those who died in uremia and those with oliguria or anuria, tended to have the lowest values. Conversely, the patients with the least nitrogen retention, who lived and had normal output of urine, tended to have normal values.

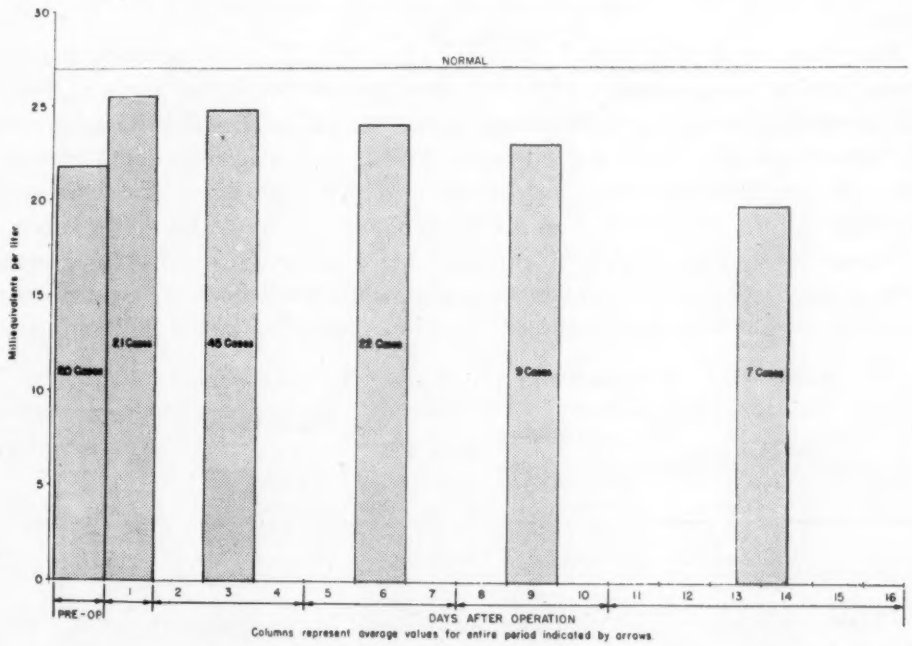

Fig. 3.—Plasma carbon dioxide combining power in azotemia.

There is no correlation of combining power with degree of shock after the preoperative day. The acidosis seen in patients in shock on admission has been discussed.[1, 2]

The evidence that a low carbon dioxide combining power is a result of diminished alkali reserve in these cases is only indirect. Blood pH's (venous)

TABLE XII

CASE NUMBER	PLASMA CARBON DIOXIDE COMBINING POWER (MEQ. PER LITER)	BLOOD pH (VENOUS)
93	16	7.31
69	23	7.39
112	20	7.04
133	21	7.32
90	20	7.37

were done in five cases that had low combining powers at the same time, and coincident renal failure. (Table XII).

From this limited number of cases in which a pH was done, and from the indirect evidence to be cited later, it seems likely that at least in the majority of cases there was a metabolic acidosis present. If the low carbon dioxide were due to respiratory alkalosis, one would expect to see clinical evidence of hyperventilation and an alkaline urine. None of our cases had either. Furthermore, in such cases the blood pH, although probably in the normal range, would be in the upper limits of normal. Obviously we do not have enough pH determinations to draw any definite conclusions, but the few we do have, which are either within the lower limits of normal or below normal, support the view that these patients in most cases were suffering from a metabolic acidosis. This was not of the hyperchloremic variety. (See the section on chlorides and sodium.)

Examination of Fig. 4 and Tables VII and XIII gives at least a partial explanation for the acidosis. After the first postoperative day none of the patients were able to make a urine more acid than pH of 6.0 despite an increasingly severe acidosis. This is even more evident in the uremic death group, in which the renal failure was most severe. Which portion of the base-saving mechanism of the kidney is responsible for this can only be conjectured, in most cases, for it was possible to measure urine ammonia or titratable acidity in only a few instances. Likewise, comparison of total anions with total cations gives little insight into the situation (see discussion of chloride and sodium).

TABLE XIII. AVERAGE URINE pH IN THE "HIGH AZOTEMIA" GROUP

	PREOPERATIVE	POSTOPERATIVE DAYS				
		1	2 TO 4	5 TO 7	8 TO 10	11 TO 16
Died in uremia	5.5 (2 cases)	5.9 ± 0.2 (9 cases)	5.9 ± 0.1 (23 cases)	6.4 ± 0.3 (12 cases)	6.4 ± 0.3 (5 cases)	6.0 (2 cases)
All cases	5.8 ± 0.2 (12 cases)	6.0 ± 0.1 (21 cases)	6.2 ± 0.1 (43 cases)	6.1 ± 0.1 (29 cases)	6.0 ± 0.1 (14 cases)	6.3 ± 0.3 (12 cases)

Plasma chlorides: The plasma chloride level in the "high azotemia" group is shown in Table VII and Fig. 5. In patients dying in uremia, an extreme hypochloremia was reached by the tenth day, if all cases are averaged; and only one of these survived after the tenth day. This group (uremic death) is not, therefore, represented in the column covering the eleventh to sixteenth days (Fig. 5). Average values for patients who lived were only slightly low during the period of greatest nitrogen retention. Analysis of individual case

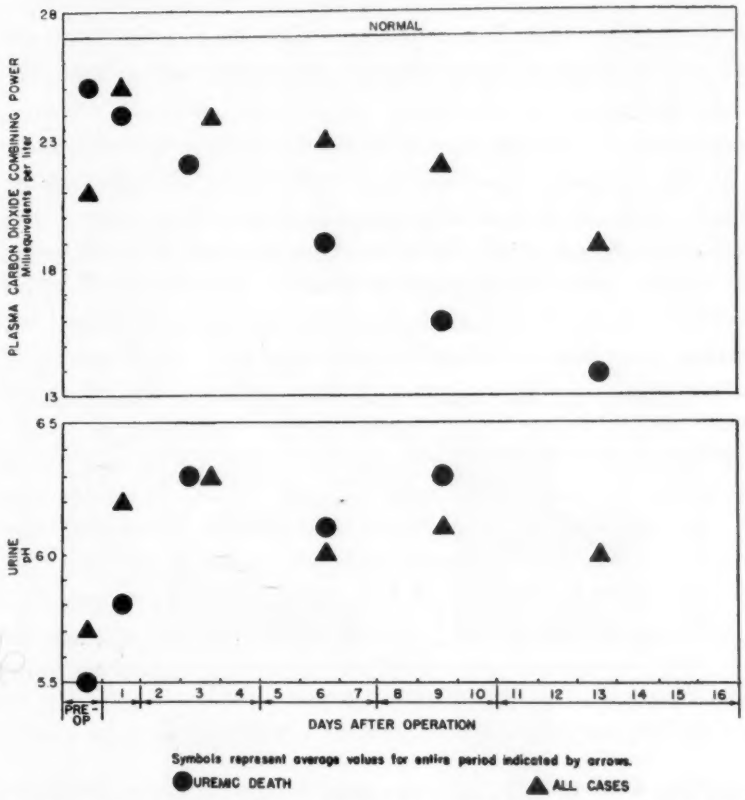

Fig. 4.—Plasma carbon dioxide combining power and pH of urine in azotemia.

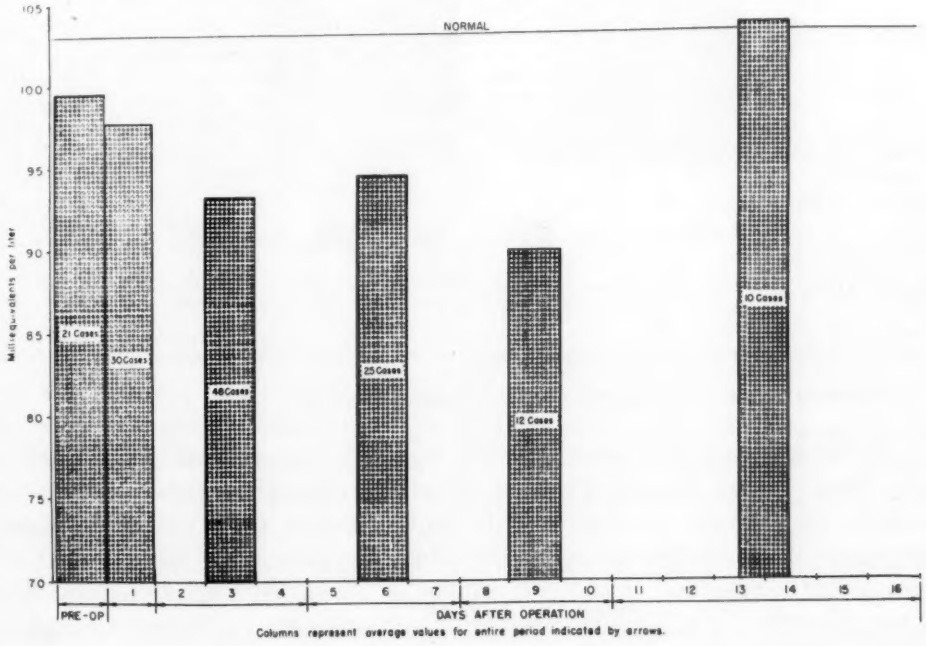

Fig. 5.—Average plasma chlorides in azotemia.

records showed that the patients with the lowest chlorides were chiefly those who died before the tenth day, and hence that the rise in the tenth to fifteenth days occurred largely in those patients who had had a recovery diuresis or minimal azotemia.[1]

Relationship of low plasma chloride levels to intake of sodium chloride: Since, with the exception of a few cases with frank alkalosis, the hypochloremia in practically all instances was accompanied by a low carbon dioxide combining power, the mechanism of this hypochloremia was of considerable interest to us. Most of the patients with a low plasma chloride were extremely ill and took practically no food by mouth. Hence, their source of salt was almost entirely derived from that administered parenterally. Comparison of the amount of parenteral sodium chloride given to the patients who presumably had the most severe renal lesions in the group (those who died in uremia) with the corresponding plasma chloride level, shows interesting correlation (Table XIV). Of 32 patients who died in uremia, 11 had normal chlorides up to the time of death. All of these 11 had received considerable parenteral sodium chloride in the previous three days. Twenty-one patients had low chlorides, under 100 meq. per liter, and of these 21, 10 had received no chlorides parenterally during the previous three days, and 11 had received on an average much less salt than those with normal plasma levels. It should be emphasized that this analysis includes only patients who died in uremia, and are, therefore, those in whom the maximum degree of renal impairment could logically be expected.

TABLE XIV. RELATIONSHIP OF PARENTERAL SODIUM CHLORIDE ADMINISTRATION TO PLASMA CHLORIDE

(a) In 32 patients who died in uremia and (b) In 19 patients who recovered (this group indicated by italics)

	TOTAL CASES	PLASMA CHLORIDE* (MEQ. PER LITER)			PARENTERAL NACL IN PREVIOUS 3 DAYS (GM. PER DAY)			NO NACL IN PREVIOUS 3 DAYS
		MAX.	MIN.	AVE.	MAX.	MIN.	AVE.	
Normal plasma chlorides†	11	111	100	104	76.5	8.5	34.4	
	7	*144*	*100*	*119*	*93.5*	*17.0*	*42.5*	
Number of cases				11			11	0
				7			*4*	*3*
Low plasma chlorides†	21	94	69	84.3	34.0	8.5	23.2	
	12	*99*	*76*	*91.2*	*51.0*	*4.2*	*26.9*	
Number of cases				21			11	10
				12			*3*	*9*

*Last determination only for Group (a) one to two days before death.
†"Normal," 100 meq. or over; "low," under 100 meq.
Patients who received no NaCl *not* included in average.

In the patients with azotemia who survived, the relationship of parenteral salt intake to low plasma chloride as not so clear-cut (Table XIV). These patients as a whole were not so ill, and probably their chloride intake by mouth was more nearly adequate; therefore the parenteral salt received is not as accurate a measure of chloride intake as in patients who died in uremia. If one consults the individual records of patients who developed marked renal failure and yet survived (see also the section on Recovery Diuresis), it would

appear that hypochloremia is part of the chemical picture in most such cases (for example, Cases 60, 27, 125)[1] but that it is to a large degree associated with the sodium chloride intake. This relationship to intake is also brought out in conjunction with the discussion of sodium (see discussion to follow and Fig. 6).

Several exceptions to these generalizations were evident in individual cases. With apparently adequate salt intake, the chloride may be low, even in cases where there was no demonstrable loss of chloride through Wangensteen drainage or vomiting. In one case with azotemia and all the other clinical features common to the syndrome of severe renal failure, the plasma chlorides were abnormally high (Case 133),[1] although here the salt intake had been excessive (Fig. 7).

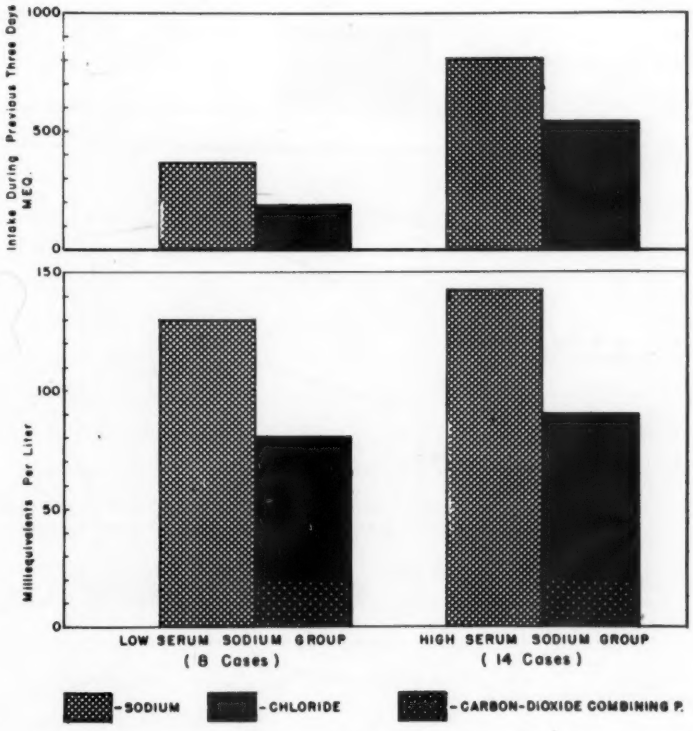

Fig. 6.—Relationship of serum sodium, plasma chloride, and carbon dioxide combining power to parenteral intake of sodium and chloride in azotemia.

It is possible that the hypochloremia might be due in part to a simple dilution of the chloride ion, for practically all of these patients had an increased plasma volume. (See discussion on Plasma Volume, to follow). No such connection, however, is apparent in Table XV, which shows plasma volume and plasma chloride determinations done simultaneously in 18 patients who died in uremia.

No correlation between degree of initial shock and plasma chloride level could be demonstrated.

Chloride excretion: Total urinary chloride excretion was measured in five patients with renal failure (Cases 104, 107, 108, 112, 133).[1] Three of these

also had severe alkalosis and are discussed in detail elsewhere.[1, 4] These three all had extremely low chloride excretion. The remaining 2 both had recovery diuresis. Chloride excretion in one (Case 104) was essentially normal, but in this instance determinations were begun after he had actually recovered. The other (Case 133)[1] is discussed in detail in the section on recovery diuresis. In brief, he had hyperchloremia, but a high "threshold" for chloride excretion (Fig. 7).

Chloride concentration of single specimens of urine was measured in 18 patients who died in uremia. In nine determinations on 8 patients with normal plasma chlorides (100 meq. or over), the average urine chloride concentration was 424.4 ± 60.2 mg. per cent. In 21 determinations on 10 patients with low

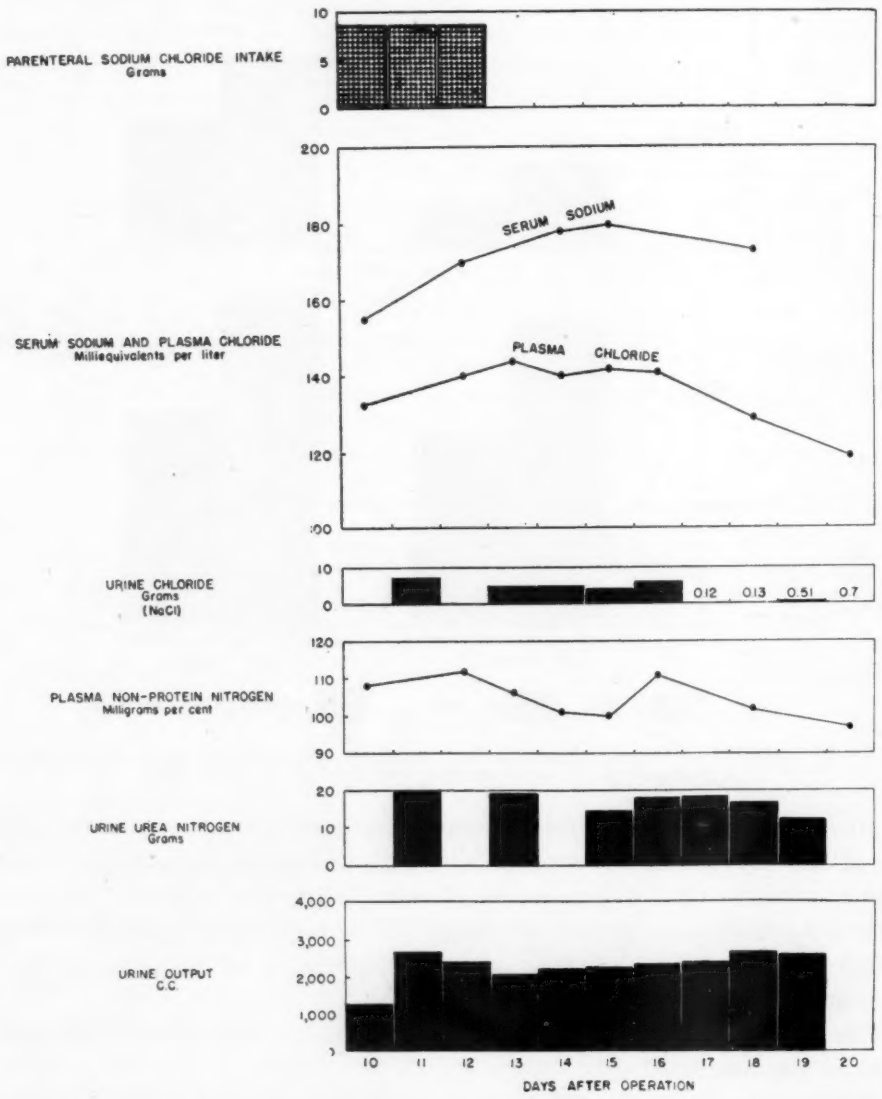

Fig. 7.—Course of patient with post-traumatic renal insufficiency and recovery diuresis. During the six days previous to those depicted, he had received 95 Gm. of sodium chloride parenterally. Note hypernatremia, hyperchloremia, very low excretion of sodium chloride in spite of chloride and sodium retention in the blood (Case 133[1]).

TABLE XV. PLASMA CHLORIDE CONCENTRATIONS AND PLASMA VOLUMES IN EIGHTEEN PATIENTS WHO DIED IN UREMIA

CASE NUMBER	DAYS POSTOPERATIVE	PLASMA CHLORIDES (MEQ. PER LITER)	PLASMA VOLUME (% INCREASE OR DECREASE)	BLOOD VOLUME (% INCREASE OR DECREASE)
9	6	72	43.9	21.0
69	8	76	23.5	15.8
86	6	76	61.4	25.5
55	7	80	95.1	37.7
47	3	82	33.6	8.8
93	6	82	22.2	6.1
118	5	82	16.3	6.1
80	4	86	10.7	−5.5
22	5	90	67.9	13.0
108	3	91	17.7	3.8
135	4	91	80.2	63.9
95	3	92	13.4	−1.0
123	3	93	52.3	18.6
52	2	93	60.1	33.5
105	7	103	61.0	39.8
136	3	104	−19.3	−14.5
26	3	106	41.5	21.8
98	5	111	33.9	32.7

plasma levels the average was 326.0 ± 41.3 mg. per cent, not a significant difference. It is difficult to say how important these single specimens are because of the well-known fact that the chloride concentration of the urine varies widely throughout a twenty-four hour period. The values in these groups of cases are undoubtedly lower than would be observed in normal individuals.

From the data presented, it can be concluded that in renal failure of the type considered here, the plasma chlorides tend in most cases to fall as renal insufficiency progresses. The degree of hypochloremia depends to a large extent on salt intake. Measurements of urinary chloride indicate that the hypochloremia is not due to excessive excretion of the chloride ion; indeed, the amount in the urine is below normal. No correlation between plasma level and increased plasma volume could be demonstrated; and therefore the low levels, as far as could be determined from our data, were not due to simple dilution.

In addition to inadequate salt intake, there must be other factors that contribute toward hypochloremia, such as a derangement of the chloride-regulating mechanism which causes a shift of chloride ions from the intravascular bed to other extracellular or intracellular reservoirs. The fact that in these patients we demonstrated an abnormally large plasma volume would support such a hypothesis, although, as stated previously, no correlation of plasma chloride level with plasma volume *per se* could be demonstrated.

Plasma phosphate: The variations in phosphorus have been discussed under another heading in more detail (see the section on nitrogenous waste products). The phosphates are mentioned here again only to indicate their relation to total acid-base balance. Reference to Fig. 1 and Table VII shows that when considered in terms of equivalence, the plasma phosphates, even when elevated to twice normal or over, make up a small proportion of the total anion column; they clearly account for only a portion of the carbon dioxide displaced in these cases.

Plasma Proteins: Plasma proteins have been converted into milliequivalents in Fig. 1 and Table VII. Inspection of these values shows a remarkable constancy with very small standard errors of the mean. Although the proteins represent a significant proportion of the total anions present, their importance in terms of change in acid-base balance is negligible.

Cations.—

Sodium: The number of sodium analyses was small in comparison with those of anions. By grouping all determinations done in the patients with azotemia between the second and tenth postoperative days (or days after trauma), however, some interesting relationships emerged (Table XVI and Fig. 6).

TABLE XVI. RELATIONSHIP OF SERUM SODIUM PLASMA CHLORIDE, AND CARBON DIOXIDE COMBINING POWER TO *Parenteral* SODIUM AND CHLORIDE INTAKE IN AZOTEMIA

	AVERAGE LEVEL (MEQ. PER LITER)			AVERAGE INTAKE DURING 3 DAYS PREVIOUS* (TOTAL MEQ.)		
	SODIUM (SERUM)	CHLORIDE (PLASMA)	CARBON DIOXIDE (PLASMA)	EXTRA SODIUM	TOTAL SODIUM	CHLORIDE
Sodium under 140 (18 cases)	130.6 ± 1.2	80.7 ± 2.0	22.9 ± 1.8	187 ± 56	369 ± 65	183 ± 54
Sodium over 140 (14 cases)	146.5 ± 1.5	95.3 ± 2.7	23.0 ± 2.0	270 ± 48	805 ± 117	541 ± 93
All cases (32)	137.6 ± 1.7	87.1 ± 2.1	22.9 ± 1.3	221 ± 39	561 ± 78	339 ± 71

*Calculated from per cent of sodium or chloride present in sodium citrate, soda bicarbonate, or sodium chloride.

The thirty-two determinations were done in 26 patients. In four instances, two determinations in the same patient on different days are included, and in one instance, three determinations on different days. Twenty-four of the determinations were in patients dying in uremia; two were in cases where uremia was contributory to death; and one was in a case where uremia was coincident with death. Five determinations were done in patients who survived, 4 of whom had marked renal insufficiency. The table represents, then, a good sample of values for the electrolytes listed in post-traumatic renal insufficiency. Nine of the 14 with normal sodium died in uremia, 3 lived but had marked renal failure, and 1 had only slight renal failure. Sixteen of the 18 with low sodium died in uremia; 2 survived but had marked renal failure.

Several important facts seem evident from these data: (1) Serum sodium and plasma chloride concentrations are chiefly dependent on intake of these ions regardless of the severity of the renal insufficiency present. (2) The acidosis, as reflected by the low carbon dioxide combining power, is equally severe in either group, regardless of the sodium or chloride level. (3) The outcome was the same in both groups; there was no evidence that the diminished sodium and chloride concentrations in the plasma affected the course of the disease.

The cause of the acidosis in these cases was puzzling. If it were due to loss of total base, one would expect a lower carbon dioxide combining power in the low sodium group; if due to substitution of chloride for carbon dioxide, the plasma chlorides should be high. As mentioned previously, phosphates are not sufficiently elevated to account for the change entirely in terms of base equivalence. Proteins remain constant and essentially normal. Sulfates and organic acids were not measured; these two components may account for some of the discrepancies evident in our data.

Magnesium: As with sodium, there were too few determinations for statistical treatment. Fourteen determinations done between the second and tenth postoperative days in 13 cases (two determinations in the same patient on different days are included) averaged 2.3 ± 0.1 meq. per liter. The nonprotein nitrogens done simultaneously averaged 164 ± 22. If these few determinations were significant, there was no evidence of abnormalities of magnesium metabolism in this type of renal insufficiency.

Potassium: Unfortunately, only a few determinations were made; these are listed in the individual case records (Cases 78, 80, 107, 112, 133, 135, 138).[1] In five of these, values were above normal (6.2 to 9.8 meq. per liter).

Calcium: See the discussion on phosphorus, under nonprotein nitrogen and phosphorus changes.

Plasma and Blood Volume

Plasma volume was determined in 23 patients at a time when they had post-traumatic renal insufficiency. The results were striking and of practical importance, for they indicated that increase in plasma volume is a part of the abnormal physiologic picture.

Referring first to Tables XVII and XXII, it is evident that in 19 fatal cases, and in these fatal cases plus 4 with recovery diuresis, the average plasma volume was increased significantly for the entire group, +41.6 ± 6.6 in fatal cases, and +43.3 ± 5.7 in all 23 cases. Average increases for those who received more than one liter of fluid intravenously daily (Group A) were much greater than for the 4 who received less than one liter daily (Group B, Table XVII). Analysis of Tables XVIII and XIX, from which the averages in Table XVII were computed, shows that no patients in Group A and only one patient in Group B had normal or subnormal plasma volumes. In this one patient (Case

TABLE XVII. PLASMA VOLUME IN NINETEEN PATIENTS WITH FATAL ANURIA AND OLIGURIA
Figures Expressed as Per Cent of Calculated, Normal, Uncorrected Plasma Volume

ALL CASES (19)		GROUP A (15 cases)		GROUP B (4 cases)	
INCREASE IN PLASMA VOLUME (AV.)	DAYS AFTER OPERATION (AV.)	INCREASE IN PLASMA VOLUME (AV.)	DAYS AFTER OPERATION (AV.)	INCREASE IN PLASMA VOLUME (AV.)	DAYS AFTER OPERATION (AV.)
41.6 ± 6.6	4.8 ± 0.4	46.9 ± 6.6	4.8 ± 0.5	21.8	4.8

Group A, Patients who received more than one liter of fluid (average) intravenous, colloid and crystalloid, per day.

Group B, Patients who received less than one liter of fluid (average) intravenous colloid and crystalloid, per day.

136) there is some reason to question whether deficient circulating blood volume was adequately replaced, and hence whether he ever really recovered from shock during the four days he survived after wounding.

TABLE XVIII. PLASMA AND BLOOD VOLUMES IN FATAL POST-TRAUMATIC RENAL INSUFFICIENCY
Group A, Patients Who Received One Liter or More of Intravenous Fluids (Crystalloid or Colloid) Daily

CASE NUMBER	DAYS	PLASMA VOLUME (%)	PLASMA PROTEINS (GM. %)	HEMATOCRIT (%)	BLOOD VOLUME (%)	BLOOD (UNITS†)	PLASMA (UNITS†)
108	1	6.7	5.1	28		11	3
	3	17.7	5.6	40	3.8	13	3
52	2		5.7	36		8	4
	3	60.1	6.2	38	33.5	8	4
55	6		6.4	27		6	6
	7	95.1	6.3	25	37.7	7	6
135	2	17.3	6.5	50	22.9	6	0
	4	80.2	7.3	42	63.9	6	0
95	1		6.5	48		10	1
	3	13.4	6.6	40	−1.0	10	5
80	3		6.5	38		8	3
	4	10.7	7.1	38	−5.5	8	3
69	1*		6.8	70		1.5	2
	2*	23.5	6.3	52	13.6	1.5	2
	5*		5.4	47		1.5	2
	9*	23.5	5.1	42	15.8	1.5	2
47	1	8.7	5.3	33		4.5	2
	3	33.6	4.8	35	8.8	4.5	2
98	5	33.9	6.6	47	32.7	8	5
9	5		7.5	36		2.2	3.3
	6	43.9	6.8	37	21	2.2	3.3
86	2	26.5	6.0	33	−0.1	8	2
	4		6.2	39		10	2
	6	61.4	6.1	32	25.5	10	2
105	7	61.0	7.3	39	39.8	3	6
114	6	75.2	5.8	30	31.9	6	1
26	3	41.5	6.9	38	21.8	4.5	6
123	3	52.3	5.8	32	18.6	7	1.3
	6		5.8	29		7.5	1.3

*Days after release from crush.
†Since wounding.

TABLE XIX. PLASMA AND BLOOD VOLUMES IN FATAL POST-TRAUMATIC RENAL INSUFFICIENCY
Group B, Patients Who Received Less Than One Liter of Intravenous Fluids (Crystalloid or Colloid) Daily

CASE NUMBER	DAYS	PLASMA VOLUME (%)	PLASMA PROTEINS (GM. %)	HEMATOCRIT (%)	BLOOD VOLUME (%)	BLOOD (UNITS†)	PLASMA (UNITS†)
93	1*	−31.4	7.3	60	−5.7	0	2
	3*		6.2	44		0	2
	6*	22.2	6.2	39	6.1	0	2
136	3	−19.3	8.0	50	−14.5	9	4
118	2	34.4	6.7	41	20.7	9	2
	5	16.3	6.6	42	6.1	9	2
22	5	67.9	7.1	21	13.0	5	3

*Days after release from crush.
†Since wounding.

Table XX gives similar data on the 4 patients who had renal insufficiency and subsequent recovery diuresis. Fig. 8 relates the plasma volume increase in 3 of them to nitrogen retention (Cases 60, 133, 138).[1] Plasma volume increased and then decreased as recovery diuresis proceeded and nitrogen waste products were excreted. The fourth (Case 150)[1] was seen for the first time after diuresis had begun although he still had marked renal failure. His plasma volume also was increased.

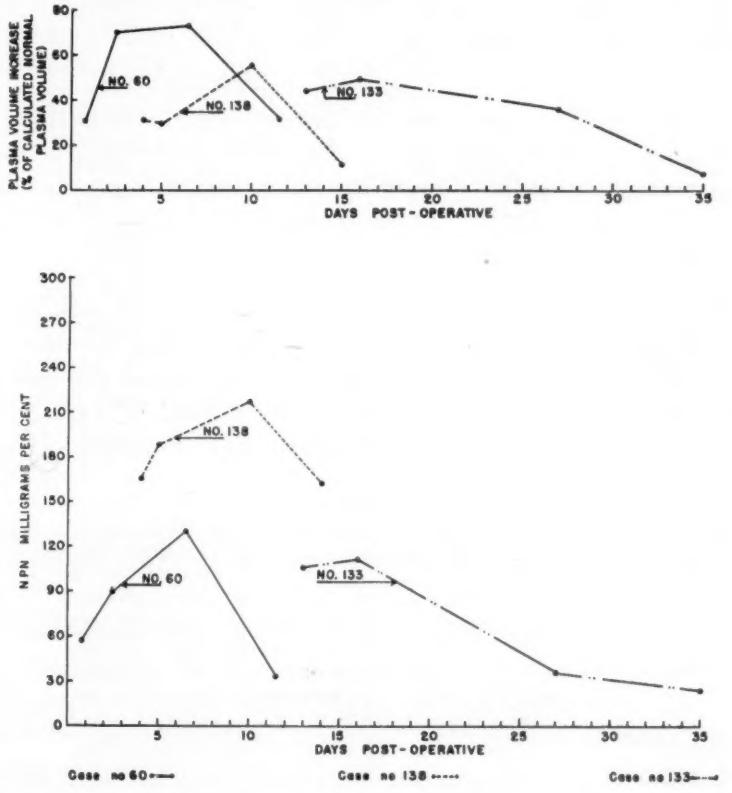

Fig. 8.—Plasma volume and plasma nonprotein nitrogen in recovery diuresis.

Table XXI represents further analysis of all 23 cases. Twenty-two had increased plasma volumes. Eighteen of these 22 received an average of more than one liter of crystalloid or colloid parenterally daily. In 10 of the 22, plasma volume was determined more than once, and in 8 of these 10, plasma volume increased with increasing renal failure. In 3 cases with recovery diuresis included with these 8, plasma volume then shrunk as renal function improved (Fig. 8, Table XX). Of the 2 whose plasma volume did not increase as renal failure progressed, one (Case 69, Table 18) was in Group A, whose average fluid intake was high. His plasma volume was increased + 23 per cent on both the second and ninth days after crushing injury. The other (Case 118, Table XIX) was in Group B, those with restricted fluid intake. His plasma volume actually diminished, although he subsequently died in uremia.

TABLE XX. PLASMA AND BLOOD VOLUME IN CASES OF POST-TRAUMATIC RENAL INSUFFICIENCY WITH SUBSEQUENT RECOVERY DIURESIS

CASE NUMBER	DAYS	PLASMA VOLUME (%)	PLASMA PROTEINS (GM. %)	HEMATOCRIT (%)	BLOOD VOLUME (%)	INTRAVENOUS (C.C.)	ORAL (C.C.)	BLOOD (UNITS†)	PLASMA (UNITS†)
60	.75	30.3	6.3	25	−8	3429		5.5	10
	2.5	70.1	6.5	25	20	1000*	1435*	7.5	10
	6.5	73.5	6.4	24	21	625*	2386*	8.5	10
	11.5	31.7	6.4	38.4	13	600*	3952*	13.5	10
133	13	44.3	7.6	40	25	2518	1750	23	10.5
	16	49.8	7.4	40	32	1583*	1416*	24	12.5
	27	36.1	6.1	32	5			26	12.5
	35	7.4	5.8	36	−12			26	12.5
138	4	30.7	6.6	40	16	?	?	2	2
	5	29.7	6.0	40	15	0	1525*	2	2
	10	55.6	6.6	32	20	1650	1160*	2	6
	14	11.1	8.0	40	−1.9	1000	2326*	2	6
150	12.5	27.3	6.0	34	1.7	1000	3330?	9.8	4

*Between determinations.
†Since wounding.

A possible explanation for the low plasma volume in the one case without increase in plasma volume (Case 136, Table XIX) has been mentioned previously.

The relationships of plasma volume to plasma protein concentration, hematocrit, and total blood volume are evident in Tables XVIII, XIX, and XX. There are considerable individual variations, but in general it can be stated

TABLE XXI

	NUMBER OF CASES	RECEIVED ONE LITER OR MORE INTRAVENOUS FLUID DAILY (AV.)	PLASMA VOLUME DETERMINATION REPEATED	TREND OF PLASMA VOLUME DETERMINATION WHEN REPEATED		OUTCOME	
				INCREASED	DECREASED OR NORMAL	LIVED	DIED
Plasma volume increased	22*	18	10	8	2	4	18
Plasma volume normal or low	1	0	0	–	–	0	1

*Four cases of recovery diuresis included.

that an expected decrease in plasma protein concentration as plasma volume increased was not usually demonstrated. Thus, of the 8 patients in whom plasma volume was known to increase, there were no significant changes in plasma protein concentration in 5 (3 of whom received blood between measurements), there was an increase in 1, and a decrease in only 2. Explanation for

TABLE XXII. PLASMA VOLUME IN TWENTY-THREE PATIENTS WITH RENAL INSUFFICIENCY

ALL CASES (23)		INCREASED PLASMA VOLUME (22 CASES)		LOW OR NORMAL PLASMA VOLUME (1 CASE)	
PER CENT CHANGE*	DAYS POSTOPERATIVE	PER CENT CHANGE*	DAYS POSTOPERATIVE	PER CENT CHANGE*	DAYS POSTOPERATIVE
43.3 ± 5.7	6.0 ± 0.7	46.2 ± 5.1	6.1 ± 0.7	−19.3	3

*Per cent of uncorrected, normal plasma volume.

the absence of a dilution phenomenon is not evident from our data. One can only postulate that in such cases plasma protein was being mobilized from protein sources elsewhere in the body. The hematocrit in the 8 patients in whom plasma volume increased (as shown by serial determinations) rose in 1 (who received blood between measurements), was unchanged in 3 (2 of whom received blood between measurements), and fell in 4 (one of whom received blood between measurements). Although the total blood volumes were also increased, the increments clearly were a reflection of the increase in the plasma volume, and because of the low hematocrits in most cases were not as strikingly increased as the plasma volume.

These data indicate, then, that in this type of renal failure total circulating plasma volume is uniformly increased. This must be due largely to the inability of the kidneys to excrete adequate water. However, because the plasma protein concentration did not usually diminish as plasma volume increased, it is evident that the sole explanation is not simply that hydremia exists. Unexplained extrarenal factors interfering with maintenance of a normal extracellular fluid volume seem also to be present. The practical importance of these observations is self-evident. Administration of excessive quantities of fluids to these patients who already have increased extracellular fluid volume can probably do nothing toward stimulating the kidneys to excrete; it can cause fatal pulmonary edema.

Changes in the Urine

Specific Gravity.—One of the most striking and constant alterations in this syndrome is seen here. Within one or two days postoperatively, the patients who developed renal failure almost without exception lost the power to make a concentrated urine regardless of the amount they were excreting (Fig. 9, Table XXIII). The averages listed in the table and those used in the figure were calculated from the specific gravities observed in routine specimens, usually the first morning specimens. They do not then, represent true concentration tests; but there are several factors which indicate that the values observed in most cases are those of practically maximum concentrating ability: (1) Concentration tests were done later on patients who recovered, when it was deemed safe to do so. In these, even after the retained nitrogenous products had been cleared and urinary output had returned to normal, specific gravity remained fixed and low for considerable periods of time. (2) Many of the specimens were taken when the urinary output was very low and hence when the kidneys

TABLE XXIII. URINE SPECIFIC GRAVITY IN THE "HIGH AZOTEMIA" GROUP

	PREOPERATIVE	POSTOPERATIVE				
		1	2 TO 4	5 TO 7	8 TO 10	11 TO 16
Died in uremia	1.033 (2 cases)	1.021 ± 0.002 (9 cases)	1.014 ± 0.001 (26 cases)	1.011 ± 0.001 (11 cases)	1.013 (4 cases)	1.011 (2 cases)
All cases	1.026 ± 0.002 (11 cases)	1.020 ± 0.001 (21 cases)	1.015 ± 0.001 (46 cases)	1.012 ± 0.001 (28 cases)	1.014 ± 0.001 (13 cases)	1.011 ± 0.001 (12 cases)

were theoretically concentrating urine to the maximum of their ability. (3) In many of the patients, particularly those who died in uremia, fluids were sharply restricted, usually to about one liter a day—further reason for assuming that the average urine specimen would be concentrated if the kidneys were capable of making it so, although this last argument may be rendered untenable by the fact that plasma volume was probably increased in most such cases. (4) Twenty-four hour urine specimens were collected in 5 patients who developed renal failure. In these the specific gravity of the total specimens showed the same trend, even though plasma nonprotein nitrogen was rising and, in 3 cases, total output of urine was diminishing.

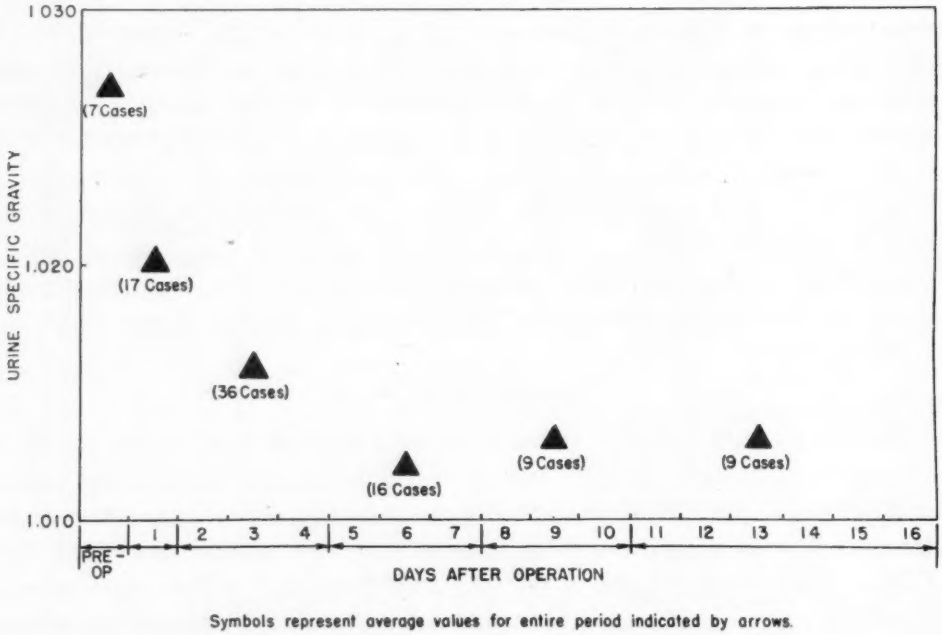

Fig. 9.—Urine specific gravity in patients with azotemia and oliguria or anuria.

These data indicate that in this syndrome one of the earliest derangements of the kidney to appear, and probably one of the last to disappear where recovery takes place, is the ability to concentrate the urine.

Hydrogen-ion Concentration.—The tendency of the acidity of the urine to decrease as metabolic acidosis and renal failure progress has been discussed (Table XIII, Fig. 4). From our meager data on measurement of titratable acidity and ammonia of the urine,[1] it seems probable that the mechanism of this failure to make a very acid urine is due to a decrease in titratable acidity, and thus is similar to that seen in most types of renal failure. Inability of the kidneys to make urine of maximum alkalinity, if presented with a surplus of base, also seems to be a feature of the syndrome,[4] and again is similar to the situation occasionally seen in other types of kidney disease.

RECOVERY DIURESIS

The reasons for choosing arbitrarily the figure of 65 mg. per cent of plasma nonprotein nitrogen as an index of renal insufficiency in this series of cases have been discussed. Of the 73 patients included in our "high azotemia" group, 23 survived (32 per cent). These 23 may be further subdivided according to the degree of renal impairment they exhibited. Twelve had apparently only minimal interference with renal function with a rapid return to normal after transient nitrogen retention. We were unable to follow one patient with a nonprotein nitrogen greater than 65, and so do not know what degree of renal insufficiency he ultimately developed. Ten had more severe and marked abnormalities and conformed with the syndrome we have designated as recovery diuresis. The characteristic features of this syndrome are the presence of (1) a nonprotein nitrogen level greater than 100 mg. per cent; (2) oliguria or anuria, followed by a substantial diuresis resulting in clearing of nitrogenous waste products and return to normal of the electrolyte pattern; (3) impaired ability to concentrate the urine; and (4) hypertension (systolic blood pressure above 135 mm. of mercury, diastolic above 90). Each of the 10 patients included showed at least three of these characteristics, and most of them showed all four. One patient (No. 44)[1] was observed during a period when we were unable adequately to examine his blood and urine; clinically, he clearly conformed with the characteristics of the syndrome.

This small group of cases is of great interest and practical importance. One would like to know, whereas the majority died, why this group recovered, and whether in their course or treatment there are any clues which might lead to more effective treatment than has been found to date. A detailed description of one or two of them, and the results of search in the group as a whole for facts pertinent to their clinical and physiologic pictures, will be presented. Complete records are presented elsewhere (Cases 27, 30, 43, 44, 60, 104, 125, 133, 138, 150).[1]

Clinical Features

The degree of initial shock was essentially the same as for the entire group that developed renal insufficiency. Three had severe shock; 5 moderate; 1 slight; and 1, no shock. As in other cases, it is quite possible that previous shock may have existed in all 10; but so far as we could determine, 2 cases had to be classified as having slight shock and no shock, respectively.

Five of these 10 patients had multiple major wounds. There were 6 peripheral wounds with fracture; 4 thoracic; 4 intra-abdominal; and 1 thoracoabdominal. There were no wounds of the liver or kidney. In one case there was contusion of the bladder.

The time of onset of oliguria in relation to wounding and operation and the duration of suppression of urinary output are of interest. Unfortu-

nately the day-to-day records were not as accurate as one would like. Many of these patients were seen in field hospitals during periods of great military activity when the press of work made it extremely difficult to make such observations. We had no record of urinary output before the first postoperative day in any of these cases. Eight of the ten patients were known to have had at least one day of oliguria or anuria between the first and fifth postoperative days. Records of urinary output were not kept for 2 patients at the time they probably had oliguria, but questioning of ward personnel and the patients suggested very strongly that they too were oliguric during this period. The duration of oliguria ranged from one to four days, then followed a period of gradually increasing output of urine, reaching in some cases 5 to 6 L. daily. The nonprotein nitrogen did not, as a rule, begin to decrease until several days after beginning of diuresis.

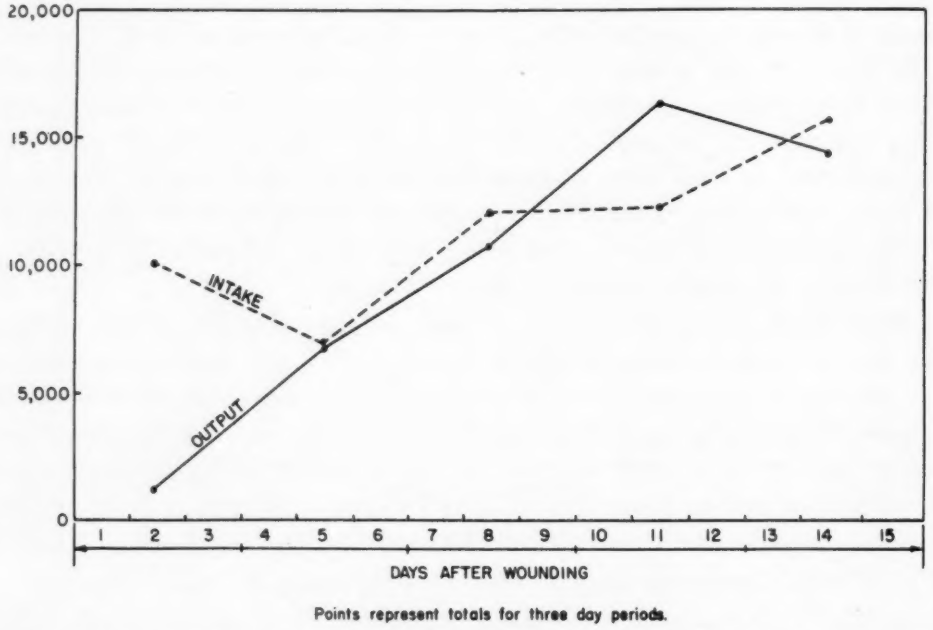

Fig. 10.—Intake and output of patient with post-traumatic renal insufficiency during course of recovery diuresis (Case 60[1]).

Because of the increase in plasma volume during the azotemic period, one would expect that total output would exceed intake during the diuresis period. This was clearly so in one case (Case 60)[1] discussed later (see Fig. 10) and in one other (Case 150).[1] In the remaining 8 cases it was impossible to demonstrate this fact from the available figures, for the records kept gave only an approximate estimate of total water balance and did not account for water lost by perspiration, respiration, or with stools. Since plasma volume returned to normal and the edema subsided as diuresis progressed, it is logical to assume that total output does exceed intake until equilibrium is again established.

All patients had hypertension, by our definition. In general, the blood pressure was highest at the time of most severe nitrogen retention and was

significantly elevated with systolic levels ranging from 150 to 170 mm. of mercury, and diastolic from 90 to 110. Likewise, as diuresis progressed and nonprotein nitrogen fell, the blood pressures returned to normal. One patient was evacuated to the rear before hypertension had subsided and we were unable to obtain subsequent blood pressure determinations.

Two patients (Cases 44 and 150)[1] had generalized convulsions on the eighth or ninth postoperative days. In one, the convulsions furnished the first clue to the attending medical officers that renal failure was present. In one of

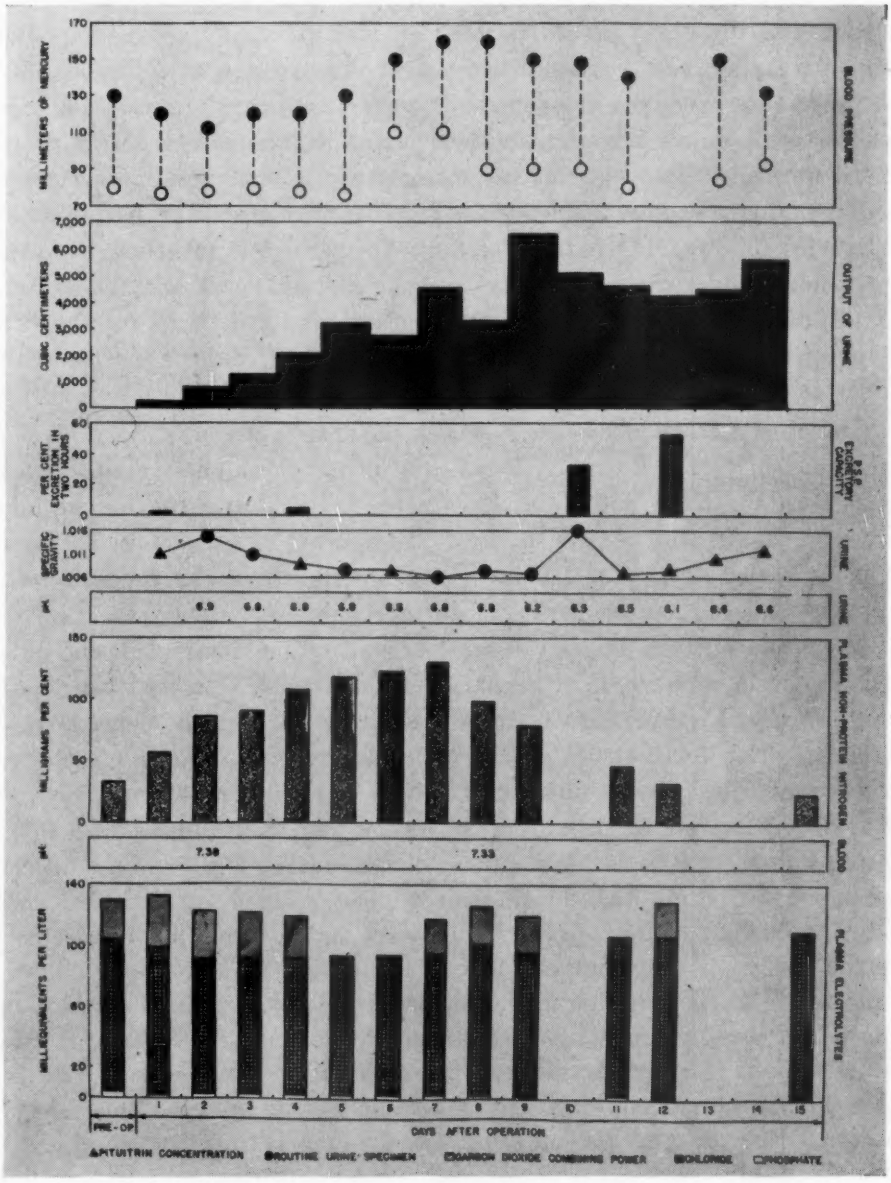

Fig. 11.—Course of patient with post-traumatic renal insufficiency and subsequent recovery diuresis (Case 60[1]).

the same two, there was a small retinal hemorrhage in the fundus of one eye. Eye grounds examined in 3 other cases were normal. In 4 cases there was clinical edema.

Blood Chemistry

The abnormal chemical pattern in this selected group of cases was essentially similar to that mentioned in the preceding section. Figs. 10 and 11 (Case 60)[1] represent the course of one man and show the essential features seen in most cases. This patient, who had had a period of severe initial shock, was oliguric for one day. Renal function, as measured by phenolsulfonphthalein excretion and the urine concentration test, was extremely reduced by the first postoperative day, and a gradual increase of urinary output followed. In spite of diuresis, however, the nonprotein nitrogen continued to rise for the first seven days—apparently because with a fixed specific gravity of the urine, the kidneys were unable to clear excess nitrogen until urine volume became great. Blood pressure rose and fell coincident with the degree of nitrogen retention. Electrolytes followed the pattern already described but returned to normal as renal function improved. Inability to make and acid urine in the presence of mild acidosis was evident. When this patient was evacuated on the fifteenth postoperative day, renal function was still reduced, despite normal chemical findings in the blood.*

The other 8 cases followed essentially the same pattern. The time of maximum nitrogen retention varied; 5 cases developed the highest nonprotein nitrogen between the third and ninth days after trauma, and the remaining four, between the tenth and thirteenth days. The period of time required for recovery hence varied from 6 to 25 days. As mentioned in the preceding section, hypochloremia was not as marked a feature in these patients as in those who died in uremia; it was present to some degree in 5 patients (plasma chlorides under 100 meq. per liter). One patient (Case 133), on the other hand, following a very high intake of sodium chloride, developed a marked hyperchloremia. The relation of plasma chloride, serum sodium, plasma carbon dioxide combining power fluid and sodium chloride intake, urinary output, and urinary excretion of chloride in this same patient are also shown in Fig. 7. After an intake of 95 Gm. of sodium chloride during the six days previous to those depicted, sodium and chloride retention developed. Plasma carbon dioxide fell, in this instance probably in part as a result of hyperchloremia. Chloride excretion was relatively low, considering the high plasma level. As the plasma level fell, choride excretion decreased to negligible amounts during the last four days, even though the amount of chloride in the plasma was still unusually high. Hypernatremia accompanied the hyperchloremia. There was, in this case, evidence of a high renal "threshold" for both sodium and chloride excretion. Specific gravities of total twenty-four hour urine specimens were uniformly dilute.

*Renal function studies done ten months later in the United States were normal.[1]

Plasma Volume

Three of four patients with recovery diuresis, whose plasma volumes were measured, had significant plasma volume increase, which was greatest at the time of maximum nitrogen retention and decreased as diuresis proceeded. They are discussed in a previous section on plasma volume, and the courses of 3 are depicted in Fig. 8. The fourth had normal blood volume when studied; this was after diuresis had started, although he still had marked renal insufficiency.

Urine Specific Gravity

Five patients, following administration of pituitrin, were unable to concentrate urine above 1.015 as long as they were followed (in one case, up to forty-nine days postoperatively). One patient with very transient nitrogen retention could concentrate to 1.020 by the thirteenth day. Concentration tests were not done in the other four, but several specimens in 3 cases were uniformly dilute. In one case (Case 30)[1] two routine specimens taken at the time of maximum nitrogen retention were 1.019 and 1,023.

Renal Clearances and Phenolsulfonphthalein Excretion

The results of tests for renal clearances and phenolsulfonphthalein excretion in patients with recovery diuresis are discussed in detail elsewhere.[3] Briefly, in 3 patients in whom clearance measurements were made, all functional components of the kidney were diminished when first observed but gradually returned toward normal over a period of several days or weeks. Similar evidence of functional impairment and subsequent improvement was seen in three patients in whom phenolsulfonphthalein excretory capacity tests were made.

TREATMENT OF POST-TRAUMATIC RENAL INSUFFICIENCY

Introduction

It should be stated at once that treatment of this syndrome once it has developed, proves disappointing. The cause of renal failure is discussed elsewhere.[1] Evidence has been presented here that shock is one factor important in the etiology; once the patient becomes available for treatment, it can usually be corrected fairly rapidly. Primary treatment should therefore be directed to the well-known principle of prompt and adequate resuscitation of every man in shock.

Our experience and recommendations in the management of patients with post-traumatic renal insufficiency, the therapeutic errors to be avoided, and the questionable use of certain drugs and procedures to stimulate renal function will be presented.

Fluid Intake

Early in the Italian campaign, fatal cases of post-traumatic renal insufficiency began to appear. Therapy almost universally consisted of intravenous administration of large amounts of various crystalloids. Practically every known diuretic was employed in some cases. In addition, attempts were often

made to render the urine alkaline by administering large quantities of available base by mouth or intravenously. In the absence of adequate urinary output, the renal insufficiency soon became complicated by cardiac failure resulting from overload of the circulation. The majority of patients died rather promptly of pulmonary edema before they could die in uremia or (as might have been the case in a few) before they could regain adequate renal function.

Early in our study it was found that the majority of patients with posttraumatic renal insufficiency had increased plasma volume, and that if more fluids were added, especially those containing sodium, water retention became even more severe. Thus, the frequency of pulmonary edema and cardiac failure is not surprising.

The therapeutic implication of such physiologic abnormality is clear. Patients with this type of renal insufficiency already have too much extracellular fluid and too large a plasma volume. The abnormality must chiefly lie in the kidneys, which are not able to excrete this surplus water. Treatment should, therefore, include measures which might encourage the kidneys to excrete more urine, but avoid any measures which would further increase plasma volume and secondarily cause cardiac embarrassment.

As described previously, the critical period in most of these cases appeared to be the first ten days. Evidence has been presented that renal function did begin to improve spontaneously about the tenth day in some patients, even though they subsequently died in uremia. The importance of avoiding an early fatal outcome as the result of too enthusiastic fluid administration cannot be overemphasized. Unfortunately, most patients later died in uremia regardless of treatment. The judicious administration of fluids at least allowed them an opportunity to recover renal function spontaneously.

We felt that the total daily fluid intake of the average patient with oliguria or anuria should not exceed 500 to 1000 c.c. Where extrarenal water losses are great, however, this allowance should be increased. If urinary output increases to more than one liter daily, fluid intake should roughly parallel urinary output until retained nitrogen is cleared. Oral fluids, where possible, are preferable to parenteral fluids in order to avoid sudden augmentation of the hydremia. What parenteral fluids are used should be administered slowly; careful observation for signs of pulmonary edema during infusion is clearly a necessity. Because of the water-retaining property of the cation in sodium chloride, we suggested that the bulk of administered parenteral fluid be 5 or 10 per cent glucose in distilled water. It now appears that by so doing, salt deprivation occurred in some cases; the outcome in those with hypochloremia, however, was not different from that in the group with normal chloride.

In patients where this regimen of fluid restriction was followed, the incidence of pulmonary edema was, in our considered judgment, materially lessened in those who subsequently died primarily of renal failure. A few who recovered might have died of heart failure had they been given quantities of fluid comparable to earlier usage.

Procedures and Drugs Used to Stimulate Kidney Function

Our experience uncovered, it may be reiterated, no positive measures capable of surely re-establishing kidney function—once renal insufficiency has developed. The aim should be to avoid measures that might be harmful before the kidneys begin spontaneously to clear retained waste products. Renal-stimulating measures that have been tried will be described briefly here.

Hypertonic Solutions.—The advisability of giving parenteral hypertonic solutions in this syndrome is highly debatable. They exert (at least in the presence of normal renal function) a diuretic effect by (1) increasing extracellular reservoirs and (2) limiting tubular reabsorption of water due to the osmotic effect of increased concentration of solute in the distal tubules. Increasing extracellular reservoirs is undesirable, since circulating plasma volume already is abnormally increased. Limiting the tubular reabsorption may be beneficent if operative in the damaged kidney.

Hypertonic saline solution except in absolute amounts of salt necessary to maintain normal levels of sodium and chloride, is contraindicated, for excessive sodium would have a prolonged and undesirable effect on extracellular fluid volume. It was used (10 per cent solution of sodium chloride) in only one of our cases.

When parenteral fluids were given, hypertonic glucose or 5 per cent glucose in normal saline solution was used in most of the cases we observed. The osmotic effect on extracellular fluid volume by solutions rendered hypertonic by sugar must be transient, lasting only until the glucose is metabolized. This type of solution also serves a nutritive function in these patients, who as a rule are eating poorly or not at all. The concentration of hypertonic glucose employed in our cases varied from 10 to 50 per cent the former being the most frequent.

There was little evidence, however, that the extensive use of these forms of hypertonic solutions had any effects upon urinary output. Since hypertonic solutions are ineffective in promoting urinary flow, and may dangerously increase blood volume, it would appear that the use of isotonic solutions is preferable. If hypertonic solutions are employed, glucose is the choice. All hypertonic solutions are contraindicated in anuria.

Alcohol.—Because of the known diuretic effect of alcohol and the suggestion that alcohol might increase renal blood flow,[5] a rather extensive trial of this agent was prompted. It was used in twenty patients who died primarily of renal insufficiency. The usual method of administration was to give it slowly intravenously, in 5 per cent solution, in total daily dosage of 50 to 100 c.c. of 95 per cent ethyl alcohol; or if the patient could tolerate it, to give 120 to 180 c.c. of whisky by mouth daily. Seven patients received approximately this dose for one day only; 9, for three to four days; and 4, for five to eight days. In a few cases the use of alcohol was followed by an increase in urinary output. Inspection of charts on fluid intake and output, however, demonstrated that many patients, even those clearly dying of renal failure, produced varying and sometimes significant quantities of urine regardless of the type of therapy em-

ployed. One might be tempted to attribute increased urinary output in a few of these twenty patients to the alcohol they received. Similar increases were found in those who received no alcohol.[1]

Two patients with recovery diuresis received alcohol, in doses comparable to those mentioned previously, and 8 others with recovery diuresis received none.

The use of alcohol produced no symptoms other than occasional mild euphoria or drowsiness.

Mercurial Diuretics.—Mercupurin was given to 3 patients who subsequently died of renal failure; 2 received 2 c.c., and the third, 1 c.c. No diuretic effect was demonstrable.

Aminophylline.—No demonstrable diuresis resulted from intravenous administration of 0.24 to 0.48 Gm. of aminophylline to 4 patients who subsequently died of renal failure.

Inorganic Ions.—The use of physiologic saline solution has been mentioned under fluid intake.

Sodium sulfate in isotonic solution (3.2 per cent) or hypertonic solution (4.2 per cent) was given to two patients in doses of 800 and 1000 c.c. respectively. No beneficial or harmful effects were noted. Both subsequently died in renal failure.

A combination of magnesium sulfate and potassium chloride was suggested as a means of reducing edema of renal tubular cells, and hence perhaps promoting urinary flow. Magnesium sulfate was used in 4 cases; 3 to 8 Gm. daily (as 50 per cent) solution intravenously and intramuscularly) were given for periods of two to five days. Plasma magnesium levels were determined in 2 of these cases—8.5 mg. per cent after 24 Gm. of magnesium sulfate in four days, in one case, and 4.6 mg. per cent after 8 Gm. in two days, in the other. This second patient received also 10 Gm. of potassium chloride (0.5 per cent solution intravenously) at about the same time. No increase in urinary output was demonstrated in these 4 patients; all later died of typical renal failure.

Although no definite symptoms of toxicity were demonstrable in these patients, the use of magnesium in such cases in the field may be dangerous. Administration of magnesium in the presence of renal failure results in rapid rise of plasma concentration of this ion. The danger of reaching toxic levels outweighs, in our opinion, any possible beneficial effect of magnesium.

We obtained no data on potassium levels reached in the one patient who received potassium chloride. This ion likewise exerts toxic effects, however, and in our opinion it should not be used. The literature gives some evidence to support the contention that retained potassium may play a lethal role in uremia.[6]

Alkalies.—The effect of alkalies in wounded patients is discussed in detail in another report.[4] Alkalies, usually in small doses, were given to many of the patients with renal insufficiency. Eleven patients who later died in uremia were given between 10 and 20 Gm. of soda bicarbonate daily for two days or more. Only in 2 of these was an alkaline urine observed. The dangers of adding sodium to the extracellular fluid have been discussed. Furthermore,

the only reason for its administration is to produce an alkaline urine, the therapeutic value of which is debatable. Despite the insolubility of certain pigment proteins in acid urine, we observed no evidence that the use of alkalies has any place in the therapy of established post-traumatic renal insufficiency; in fact, their use may cause further harm.

Spinal Anesthesia.—High spinal anesthesia was performed in two cases (Cases 47 and 135).[1] In neither was a diuretic effect noted.

Kidney Decapsulation, Sympathectomy.—Kidney decapsulation and sympathectomy were performed in one case (Case 129)[1] fifty-four hours after initial operation, during which time he had put out 150 c.c. of urine. The right kidney was decapsulated and a periarterial sympathectomy performed. No effect was expected; none was obtained. He died in uremia forty-eight hours later, having excreted 180 c.c. of urine after this second operation.

Correction of Anemia

In cases where whole blood transfusions were indicated for the correction of severe anemia, these were given. Relatively freshly stored blood was used to avoid possible pigment insult secondary to intravascular hemolysis of aged cells. No benefit or detriment to the already failing kidney was observed.

SUMMARY

The changes that begin to occur in the internal environment soon after trauma have been described in a preceding report.[1, 2] The consequences of these early changes upon the kidney have been reported herein. A man who has undergone severe trauma and the accompanying shock can be adequately resuscitated and successfully operated upon. The latent renal incompetency in this man, whose kidneys were normal prior to wounding, usually does not become manifest until two or three days after wounding. At this time there appear signs of failure on the part of the kidneys to withstand the initial insult, the effects of which thus far his body has resisted with fair success.

The first clinical sign of impending renal failure in the majority of patients is suppression of urinary output. Of 73 patients with "high azotemia" (a plasma nonprotein nitrogen level of 65 mg. per cent or higher at some time during their course), 27 had anuria (daily output of 100 c.c. or less) and 29 had oliguria (100 to 600 c.c. daily).

Mortality was high. Fifty patients (69 per cent) of 73 with "high azotemia" died. Twenty-one (47 per cent) of 45 with oliguria, and 30 (91 per cent) of 33 patients with anuria had a fatal outcome.

Initial shock was observed in a large proportion of our cases (if one excludes special types of cases such as crush injuries, reaction to incompatible blood transfusion, and sulfathiazole crystalluria). Thus, 86 per cent of the "high azotemia" group, 73 per cent of the oliguria group, and 76 per cent of the anuria group had moderate or severe initial shock. These figures are undoubtedly too low, for many men probably had shock before we saw them.

Death occurred within the first ten days after wounding in 48 of 51 patients (94 per cent) with fatal post-traumatic renal insufficiency. If the wounded man can withstand this critical period, apparent recovery of renal function begins, and he may survive. Evidence of this returning renal function appeared in a few of our patients toward the end of their course, though they subsequently died in uremia. The importance of this fact should be emphasized, for therapeutic errors (such as overload of circulatory system by injudicious fluid administration) during this critical period may cause the fatal outcome before natural recovery can begin to take place.

Hypertension (systolic level of 135 mm. Hg or over, and diastolic level of 90 mm. Hg or over) occurred in 62 per cent of the "high azotemia" group and in 79 per cent of the uremia fatalities within this group. Many of the patients who did not develop blood pressure elevation died within four days after wounding. Had they survived longer, probably they too would have developed hypertension.

The important biochemical and physiologic abnormalities in the blood resulting from post-traumatic renal insufficiency are nitrogen and phosphorus retention, acidosis, hypochloremia, and increase in plasma volume. These blood and plasma changes reflect rapidly diminishing renal function, as indicated by inability to concentrate the urine, by frequent failure to make a highly acid or alkaline urine in the presence of metabolic acidosis or alkalosis, by diminishd glomerular filtration and renal blood flow, and by decreased phenolsulfonphthalein and maximum tubular excretory capacity of para-amino hippuric acid.

The levels of plasma nonprotein nitrogen, urea, creatinine, uric acid, and phosphorus rose as renal failure progressed during the first ten days after wounding. Most of the observations made after this period were in patients who recovered. These levels fell between the tenth and fifteenth days.

A progressive, fairly severe acidosis was characteristic, manifested by falling plasma carbon dioxide combining power as renal failure progressed. A loss of ability to make a highly acid urine in most cases suggested that the acidosis could partially be explained by impairment of the mechanism which produces an acid urine. There was also good evidence that excretion of sodium in the form of sodium bicarbonate was poorly effected in those cases in which alkalosis resulted from excessive administration of base.

Hypochloremia was severe and progressive, if all fatal cases are considered. Correlation of plasma chloride level and sodium chloride intake, however, demonstrated that the low chlorides were largely a result of inadequate salt intake. Serum sodium levels showed similar correlation. There was no difference in mortality between the hypochloremic and the normal chloride groups. One patient with renal failure had severe sodium and chloride retention following a high salt intake. Variations in plasma chloride levels were not entirely accounted for by intake. No correlation with degree of hydremia was apparent, but it was suggested that, in addition to the demonstrated relation to intake, some interference with water and sodium chloride equilibrium was present.

Phosphates, in terms of acid equivalence, contributed toward but did not entirely account for, the acidosis. Plasma proteins, if converted to milliequivalents, were normal and constant. Sulfates and organic acids were not measured, but possibly could account for discrepancies in our anion determinations.

Cation determinations were few. It has already been stated that sodium levels were correlated with salt intake. Magnesium was not significantly elevated in most cases. Potassium was determined in too few cases for conclusions. Calcium, in the few cases where determined, showed a reciprocal relationship to rising phosphorus levels.

Total plasma volume was significantly elevated in 22 of 23 patients with post-traumatic insufficiency. Nineteen of these 23 died. Three patients with severe renal failure but with recovery diuresis had plasma volume increases, which reached a maximum at the time of greatest nitrogen retention and decreased after diuresis. The degree of plasma volume increase was clearly related to fluid intake. The water retention appeared to be largely a result of administration of more fluid than the impaired kidneys could excrete. Comparison of plasma volume to total blood volume indicated that it was the plasma which was increased, rather than all elements of the blood. The expected dilution of plasma proteins was not demonstrated in most cases. The practical importance of this physiologic abnormality has been mentioned.

Ability to concentrate the urine diminished rapidly as the syndrome progressed, and specific gravity became fixed in all patients with any marked degree of renal failure. In patients who recovered it was the last function of the kidney, that we measured, which returned to normal. Since urine concentration probably takes place lower down the nephron than does excretion of mannitol, para-amino hippuric acid, or phenolsulfonphthalein, the lag in recovery of water reabsorptive capacity may point to greater relative functional impairment of the lower nephron.

Ten of the 73 patients with "high azotemia" exhibited all the features of severe renal failure, but they subsequently developed a diuresis and recovered. This fact re-emphasizes the importance of avoiding early fatal therapeutic errors, thereby affording the kidneys an opportunity for spontaneous recovery.

Therapy of post-traumatic renal insufficiency is chiefly one of prevention —early and adequate resuscitation of all patients suffering from shock. Once renal failure develops, the avoidance of the therapeutic error of administering too much fluid and hence accentuating an already increased plasma volume becomes of prime importance. Types and amounts of fluids to be administered during the period when renal failure is most severe (usually the first ten days after trauma) have been recommended. No success has been met with in the use of drugs and procedures directed toward the promotion of urine flow or the improvement of kidney function. These unsuccessful measures included the use of hypertonic solutions alcohol, mercurial and xanthine diuretics, solutions of various inorganic ions, spinal anesthesia, and decapsula-

tion of a kidney. The essential feature in therapy appears to be that of tiding the kidneys and the organism over the critical period until natural recovery takes place. Procedures, such as peritoneal lavage, which attempt to remove waste products by routes other than the kidneys until these organs resume their function, offer possibilities untried by us.

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IV. EFFECTS AND USE OF ALKALIES IN TRAUMATIC SHOCK

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THE use of alkalies has been recommended by some as an adjunct to the treatment of shock for two reasons. First, it was proposed as a means of combating acidosis known to exist in shock; second, it was suggested that production of alkaline urine might make more soluble abnormal blood or muscle pigments and sulfonamides as they were excreted in the urine. Evidence will be presented here that with judicious use of alkalis it is possible to relieve metabolic acidosis, but that in the presence of shock and accompanying decrease in renal function it may be very difficult and even dangerous to attempt to produce an alkaline urine.

Any patient who receives blood or blood substitutes, of necessity gets sodium citrate, which is employed as anticoagulant when the blood is collected from the donor. Although the amount varies slightly, we have assumed that each unit of blood or plasma contains 2.0 Gm. of U.S.P. sodium citrate. The amount of alkali given to a patient who receives several liters of blood or plasma is therefore considerable.

When additional alkali was given in the cases we observed, 2 per cent soda bicarbonate solution was the one usually employed. This was prepared by adding the soda bicarbonate to distilled water just as it was removed from the autoclave. Although some sodium carbonate undoubtedly resulted from this procedure, no untoward reactions were encountered in a large series of patients to whom this solution was given intravenously. Sodium citrate, 4 or 2.5 per cent, in sterile ampules, was also employed in a few instances.

The sodium administered in excess of that given as sodium chloride was calculated from the amount present in sodium citrate or soda bicarbonate. This figure furnished a convenient index of total alkali received, since both citrate and bicarbonate were frequently administered.

In Table I the effect of increasing amounts of alkali in relation to the degree of initial shock is shown. Those patients who received between 1.0 and 5.0 Gm. of sodium (approximately 5 to 20 Gm. of sodium citrate or soda bicarbonate) still had an acid urine after twenty to thirty hours and showed no remarkable rise in plasma carbon-dioxide combining power.

Those who received between 5.1 and 10.0 Gm. of sodium developed an alkaline urine only if they had slight or no initial shock. There was a signifi-

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TABLE I. RELATIONSHIP OF SODIUM INTAKE AND DEGREE OF INITIAL SHOCK TO PLASMA CARBON-DIOXIDE COMBINING POWER AND pH OF URINE

SODIUM INTAKE (GM.)	DEGREE OF SHOCK	PREOPERATIVE		POSTOPERATIVE			
		PLASMA CO_2 (MEQ. PER L.)	URINE pH	PLASMA CO_2 (MEQ. PER L.)	HOURS AFTER WOUNDING	URINE pH	HOURS AFTER WOUNDING
1.0 to 5.0	None or slight	24.0 ± 1.3 (6 cases)	5.9 (4 cases)	31.0 (2 cases)	21.5 (2 cases)	6.8 ± 0.24 (7 cases)	26.4 ± 4.4 (7 cases)
	Moderate or severe	24.2 ± 1.4 (9 cases)	5.7 (2 cases)	26.0 ± 2.1 (7 cases)	32 ± 3.8 (7 cases)	6.2 ± 0.13 (10 cases)	31.7 ± 4.0 (10 cases)
5.1 to 10.0	None or slight	24.0 ± 1.7 (6 cases)	5.6 (3 cases)	24.0 ± 1.8 (6 cases)	27.5 ± 3.5 (6 cases)	7.2 ± 0.22 (9 cases)	25.8 ± 3.1 (9 cases)
	Moderate or severe	21.3 ± 1.7 (12 cases)	5.9 (4 cases)	25.5 ± 1.8 (8 cases)	25.1 ± 1.6 (8 cases)	6.1 ± 0.12 (14 cases)	24.1 ± 1.6 (14 cases)
10.1 to 15.0	None or slight	25		26	29	7.4	29
		26	5.8	33	17	8.0	15
	Moderate or severe	19	5.9	25	34	6.7	34
		11	--	25	39	5.6	33
		23	5.6	--	--	6.7	33
		22	5.5	34	35	5.4	28
15.1 to 20.0	Moderate or severe	15	6.1	33	26	5.5	26
		26	--	26	24	8.1	24

The preoperative specimens were taken when no alkali, or very small amounts, had been given; the postoperative specimens were taken after the patients had received the amount of alkali indicated in the first column. The time between wounding and taking the postoperative specimens is indicated. Enough patients received between 1.0 and 10.0 Gm. of sodium to permit statistical analysis; individual figures are shown for those who received between 10.1 and 20.0 Gm.

The grams of sodium intake were calculated from percentage of sodium in sodium citrate or soda bicarbonate. It was assumed that each unit of blood or blood substitute contained 2.00 Gm. of U. S. P. sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$). Sodium administered in normal saline solution is not included in the table; therefore, only that alkali administered which becomes available as extra cations is considered here.

TABLE II. EFFECT OF ALKALI IN A PATIENT WHO DIED OF POST-TRAUMATIC RENAL INSUFFICIENCY (CASE 108)[1]

	PARENTERAL INTAKE		PLASMA CO_2 (MEQ. PER L.)	URINE pH	PLASMA Cl (MEQ. PER L.)	URINE NaCl (GM. PER 24 HR.)	PLASMA N.P.N. (MG. %)	URINE SPECIFIC GRAVITY	URINE UREA N (GM. PER 24 HR.)	URINE OUTPUT (C.C.)
	Na (MEQ.)	Cl (MEQ.)								
Preoperative (18 hr.)	811	300	22	5.5	100	0.04	37	0.13	1.032	100
First postoperative day	417	300	34	5.4	97	0.26	77	0.54	1.014	185
Second postoperative day	115	75	30	5.4	96	--	113	--	1.012	155
Third postoperative day	--	--	23	7.6	91	--	170	--	--	--

cant change in preoperative and postoperative plasma carbon dioxide only in those who had moderate or severe shock, but the urine in these cases remained acid.

Inspection of individual patients who received between 10.1 and 20.0 Gm. of sodium shows that of six with moderate or severe shock, only one was producing an alkaline urine twenty to thirty-five hours later. The two patients with no shock or slight shock both had alkaline urines. Plasma carbon dioxide rose significantly in five cases of seven in which postoperative carbon-dioxide determinations were done.

These observations show rather clearly that in patients with severe or moderate shock, even after administration of large amounts of alkali, an alkaline urine is not usually produced, although the metabolic acidosis may be relieved.

The dangers of producing severe alkalosis in such patients, and a partial explanation of their inability to form an alkaline urine, become apparent in

TABLE III. EFFECT OF ALKALI IN A PATIENT WITH SEVERE SHOCK, SUBSEQUENT NITROGEN RETENTION, AND RECOVERY (CASE 112)[1]

	PARENTERAL INTAKE		BLOOD pH (VENOUS)	PLASMA CO_2 (MEQ. PER L.)	URINE pH	PLASMA Cl (MEQ. PER L.)	URINE NaCl (GM. PER 24 HR.)	PLASMA N.P.N. (MG. %)	URINE SPECIFIC GRAVITY	URINE OUTPUT (C.C.)
	Na (MEQ.)	Cl (MEQ.)								
Preoperative (21.5 hr.)	400	0	7.04 to 7.45	20 to 30	5.4 to 6.5	99		40	1.025	530
First postoperative day	0	0	7.45	32	7.1	86	0.43	53	1.010	2180
Second postoperative day	0	0	--	36	7.2	87	1.4	67	1.010	1945
Sixth postoperative day	--	--	--	--	--	--	--	57	--	--
Twelfth postoperative day	--	--	--	--	--	--	--	34	--	--

Tables II, III, IV, and Figs. 1, 2, and 3, which depict the sequence of events in three patients with moderate or severe shock who received large amounts of alkali.

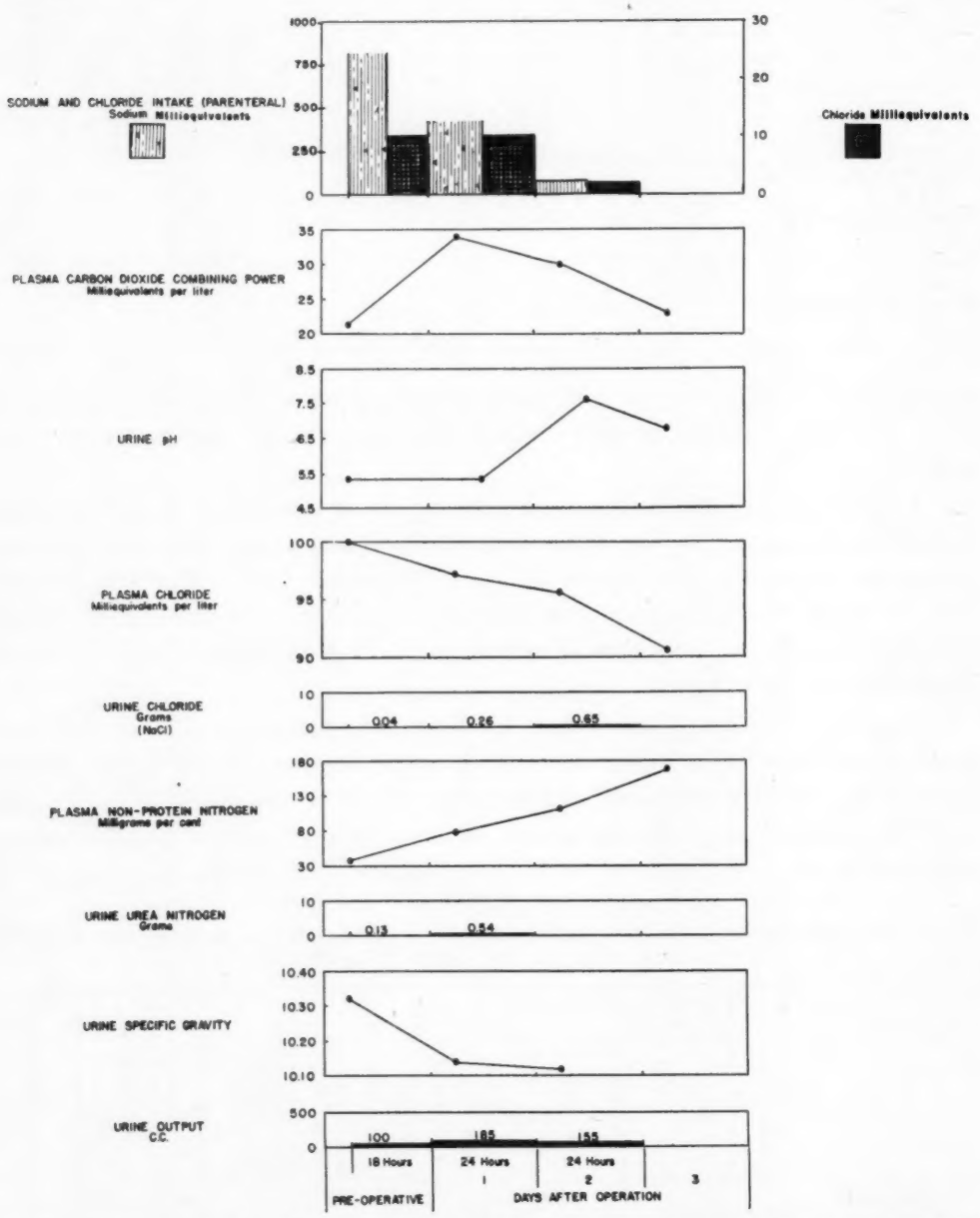

Fig. 1.—Effect of alkali in a patient who died of post-traumatic renal insufficiency (Case 108[1]). The findings are discussed in the text. Note the lag in development of an alkaline urine in the presence of a relative alkalosis.

The first patient (Table II and Fig. 1, Case 108[1]), who had severe initial shock, received 34 Gm. of soda bicarbonate and 24 Gm. of sodium citrate within the first twenty-four hours after entering the hospital. Plasma carbon dioxide responded to this excess alkali by rapidly rising to 34 meq. per liter, but in

spite of this relative alkalosis the urine did not become alkaline until the second postoperative day. Plasma chloride fell in spite of practically no urinary chloride excretion. Coincident with these changes in acid-base metabolism, urine output was very small, specific gravity of urine fell, plasma nonprotein nitrogen

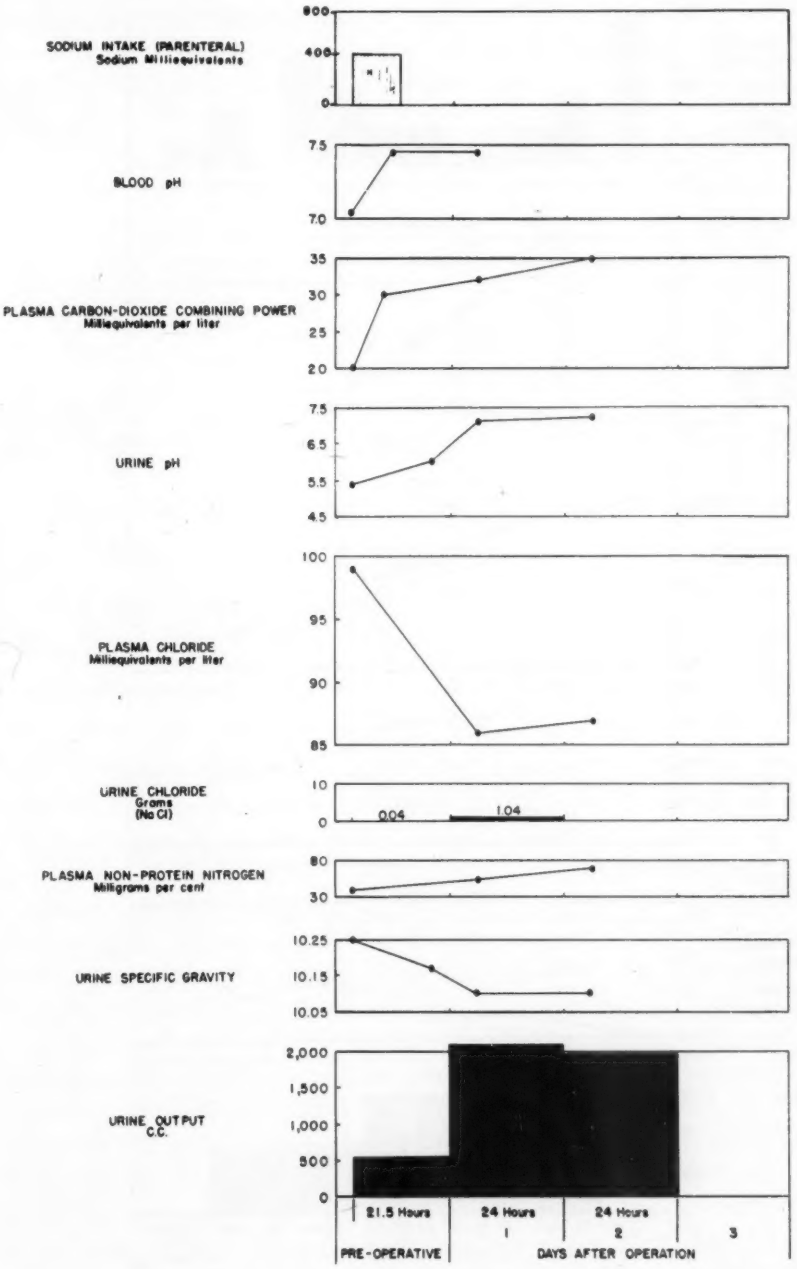

Fig. 2.—Effect of alkali in a patient with severe shock, subsequent nitrogen retention, and recovery (Case 112[1]). The findings are discussed in the text. Note: (1) Rapid metabolic response to alkali, but delayed production of an alkaline urine; (2) continued alkalosis as long as followed; (3) low plasma chlorides and low urinary chloride excretion; (4) nitrogen retention; and (5) adequate urine output but low specific gravity, and hence the rising plasma nonprotein nitrogen.

rose, urea nitrogen excretion was minimal, and the patient died in uremia on the third postoperative day.

The second patient (Table III and Fig. 2, Case 112[1]) received 20 Gm. of soda bicarbonate and 16 Gm. of sodium citrate within six hours after entering

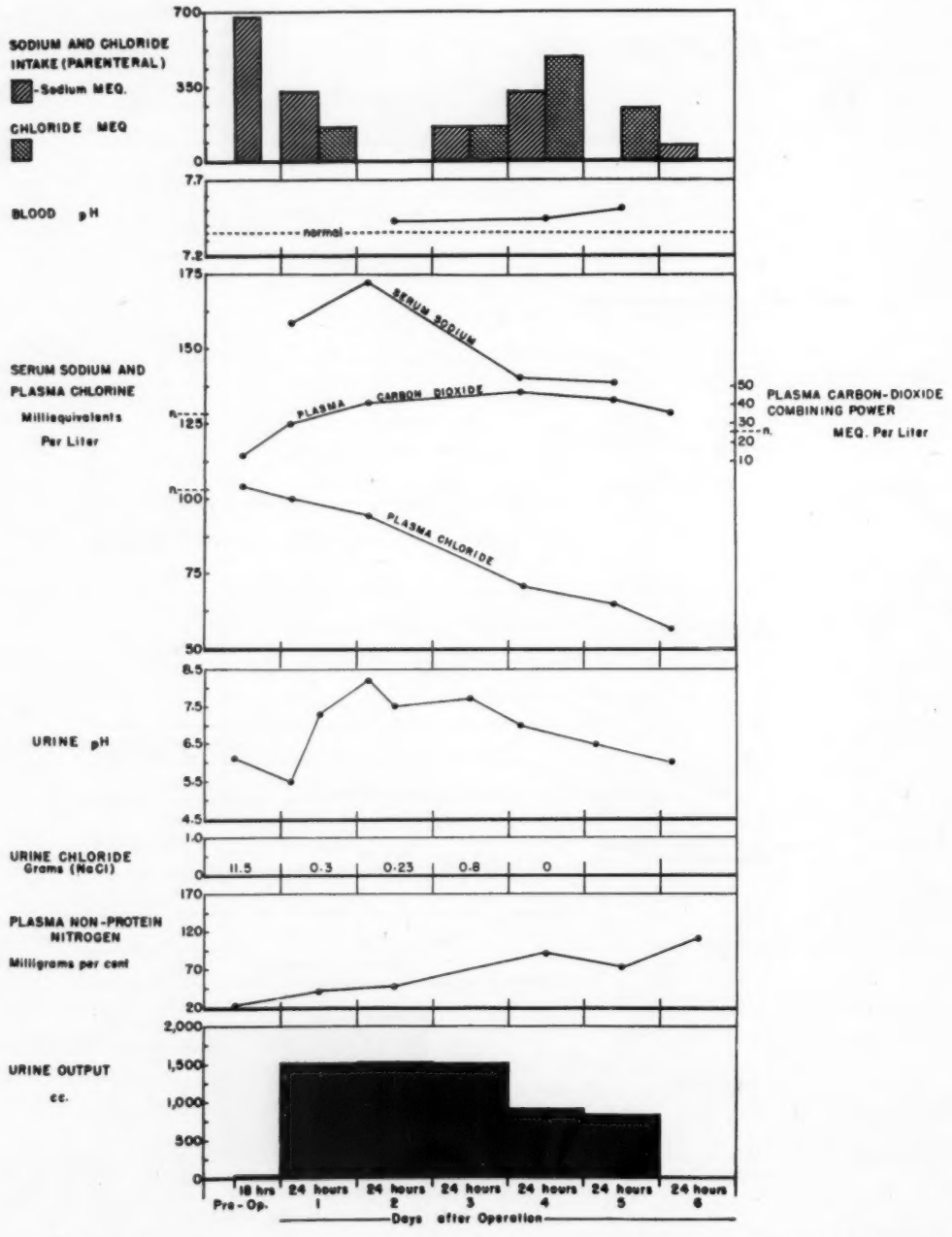

Fig. 3.—Effect of alkali in a patient with moderate initial shock, postoperative alkalosis, azotemia and death (Case 107[1]). The findings are discussed in the text. Note: (1) The lag in development of alkaline urine in the presence of alkalosis and sodium retention, and inability to excrete excess sodium, as evidenced by fall in urinary pH after the second postoperative day; (2) falling plasma chlorides, but negligible urinary chloride excretion; (3) rising plasma nonprotein nitrogen and falling urine output. Specific gravity was also fixed in this case.

the hospital in severe shock. Blood pH and plasma carbon-dioxide combining power promptly rose to levels suggesting alkalosis, but the urine was not alkaline until nearly twenty-four hours after the administration of alkali. Although urine output was normal after the first day, nonprotein nitrogen rose to 67 mg. per cent by the second postoperative day, when the patient had to be evacuated. Subsequent follow-up revealed that nitrogen retention persisted for ten days; the status of the acid-base metabolism could not be followed. Plasma chlorides likewise fell in this case, and chloride excretion was very low.

TABLE IV. EFFECT OF ALKALI IN A PATIENT WITH MODERATE INITIAL SHOCK, POSTOPERATIVE ALKALOSIS, AZOTEMIA, AND DEATH (CASE 107)[1]

	PARENTERAL INTAKE		SERUM Na (MEQ. PER L.)	PLASMA CO_2 (MEQ. PER L.)	PLASMA Cl (MEQ. PER L.)	URINE pH	URINE NaCl (GM. PER 24 HR.)	PLASMA N.P.N. (MG. %)	URINE OUTPUT (C.C.)
	Na (MEQ.)	Cl (MEQ.)							
Preoperative (18 hr.)	681	0	--	15	103	6.1	--	27	60
First postoperative day	324	146	160	30.2	100	5.5 to 7.3	--	41	1560
Second postoperative day	0	0	170	41	91	8.2	0.3	46	1570
Third postoperative day	146	146	--	--	--	7.7	0.23	--	1540
Fourth postoperative day	332	482	160	47	73	6.8	0.8	91	875
Fifth postoperative day	0	245	140	43	65	5.8	0.0	73	800
Sixth postoperative day	60	0	--	37	56	7.3	--	152	200(?)

The third patient (Table IV and Fig. 3, Case 107[1]), admitted in moderate shock, received 35 Gm. of soda bicarbonate and 28 Gm. of sodium citrate on the day of operation, and 15 Gm. more of soda bicarbonate early on the first postoperative day. The resulting severe and prolonged alkalosis was evident in the high plasma carbon dioxide and blood pH, in spite of considerable ammonium chloride given on the fourth and fifth postoperative days. Here also there was a marked lag in the production of an alkaline urine after metabolic alkalosis appeared. By the fourth postoperative day, although severe alkalosis persisted, the patient was no longer able to excrete an alkaline urine. Plasma chlorides fell to phenomenally low levels in this case (56 meq. per liter on the day before death); urinary chloride excretion was practically zero throughout the course. The nonprotein nitrogen rose, and he died with renal failure as an important contributory factor, in our opinion, on the sixth postoperative day.

The low plasma chlorides in all three of these cases are probably explained on the same basis as in other cases described elsewhere,[1, 2] and also by the fact that in the presence of high plasma carbon dioxide there has been a compensatory fall in plasma chloride. That this is not the entire explanation is evident in the fact that in two cases (Tables II and III, Figs. 1 and 2) the plasma chloride continued to fall after plasma carbon dioxide had also begun to decrease.

SUMMARY AND CONCLUSIONS

The arguments in favor of the use of alkalies in shock are: (1) to relieve metabolic acidosis and (2) to produce an alkaline urine. In our experience large amounts of alkali are necessary to relieve acidosis where severe, that is, in patients with shock. If, in addition, enough extra base is given to produce an alkaline urine in these same patients, the margin of safety between normal acid-base equilibrium and an uncompensated alkalosis may be very small. In the event that alkalosis does result, it may contribute materially toward renal failure. Three instances in which this situation may have occurred have been presented.

The mechanism of the low alkali tolerance in these patients is probably similar to that occasionally evident in other types of renal insufficiency; the impaired ability of the kidneys to excrete excessive amounts of sodium as soda bicarbonate is associated with the over-all decrease in renal function which probably exists in all patients suffering from shock, and even for some time after shock is relieved.[1, 3]

Because evidence that an alkaline urine does prevent renal complications in the type of patient we have studied is so scanty, and because of the previously mentioned dangers inherent in trying to produce an alkaline urine, we do not recommend giving alkali for the purpose of raising pH of the urine as a therapeutic procedure. Smaller amounts of alkali, sufficient to relieve metabolic acidosis, if judiciously employed are probably advisable. The obligatory amount of alkali given with blood or blood substitutes will in most instances be adequate for this purpose.

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Book Reviews

Diseases of the Chest With Emphasis on X-ray Treatment. By Eli H. Reuben. Philadelphia, 1947, W. B. Saunders Company.

From the title of the book, one would imagine that most of the consideration would be of roentgenology. This is certainly not so, because, although the roentgenographic examination of chest lesions is emphasized, the consideration of the various disease entities in the chest is taken up from every standpoint, which, of course, makes the book more valuable. The first two chapters are devoted to the anatomic consideration of the normal roentgenographic findings of the chest and the technique of x-ray examination. The third chapter is an excellent one on respiration in health and disease. This is concerned largely with physiology of respiration and methods of examination, such as vital capacity, bronchospirometry, and the importance of each of these. Another chapter is devoted to the symptoms and physical findings of chest diseases in general, with emphasis upon the necessity of obtaining a good history and getting a complete physical examination.

The various disease processes affecting the lung are then taken up in detail, giving the etiology, clinical findings, and roentgenographic findings as far as diagnosis is concerned and the treatment. An interesting part of the work are the colored illustrations by Netter. Although some are diagrammatic, they are excellent and demonstrate the points very well. Following each chapter is an excellent bibliography containing the subject material discussed within that chapter. Interspersed in the chapter are many roentgenograms showing the x-ray changes found in the particular condition being discussed. These are reproduced very well.

Tuberculosis is particularly well handled. An entire chapter is devoted to the epidemiologic considerations of tuberculosis. The fact that practically one-fourth of the whole book is devoted to tuberculosis shows the relative importance of this disease and the complete manner with which it is considered.

The final section of the book is devoted to principles of surgical treatment, in which the surgical therapy of the various conditions are considered somewhat in detail. The book is excellently done and because of its completeness should be a reference book in every library.

Grandes Problemas de Clinica Quirurgica. By Alfredo Velasco S. Paper. Pp. 431, with 33 illustrations. Santiago, Chile, 1945, Central de Publicaciones.

This South American textbook of surgery is a collection of lectures given to students by the author and collaborators. The work reflects the views and experience of the group at the Clinic of Professor Alvaro Covarrubias of Santiago, Chile.

Beginning with a lengthy discourse on infection in general, it covers a wide variety of surgical subjects under thirty-one chapter headings such as acute appendicitis, goiter, fractures of the neck of the femur, Buerger's disease or thromboangiitis obliterans, cancer of the thyroid, etc. Over one quarter of the book is devoted to infection, with the result that many subjects of considerable surgical significance are not even mentioned. Among the conditions omitted are breast disease; cancer of the lung and other surgical diseases of the lung with the exception of hydatid cyst of the lung; surgical affections of the mediastinum, heart, and pericardium; herniation; and preoperative and postoperative care. The various chapters are not in order so that certain subjects, such as orthopedics, are dispersed throughout the book. The book has an excellent table of contents but lacks a subject index. Every subject discussed is followed by a pertinent summary but no references are given.

The authors have used a novel approach in that most chapters begin with an illustrative case of the condition about to be discussed; this device enables the student to grasp quickly the problems that arise in the management of such a case and heightens the interest in the subsequent discussion. The work is written in a delightful conversational style and it aims to teach the student to observe, think, and reason things out for himself.

The best chapters in the book are those dealing with the thyroid gland and its diseases. The material is quite up to date and offers a concise review of the latest advances in this field. About the only inaccurate statement found in this section is that aberrant thyroid tissue is of no importance. Most surgeons now feel that aberrant thyroid tissues, especially lateral aberrants, are likely foci of malignancy.

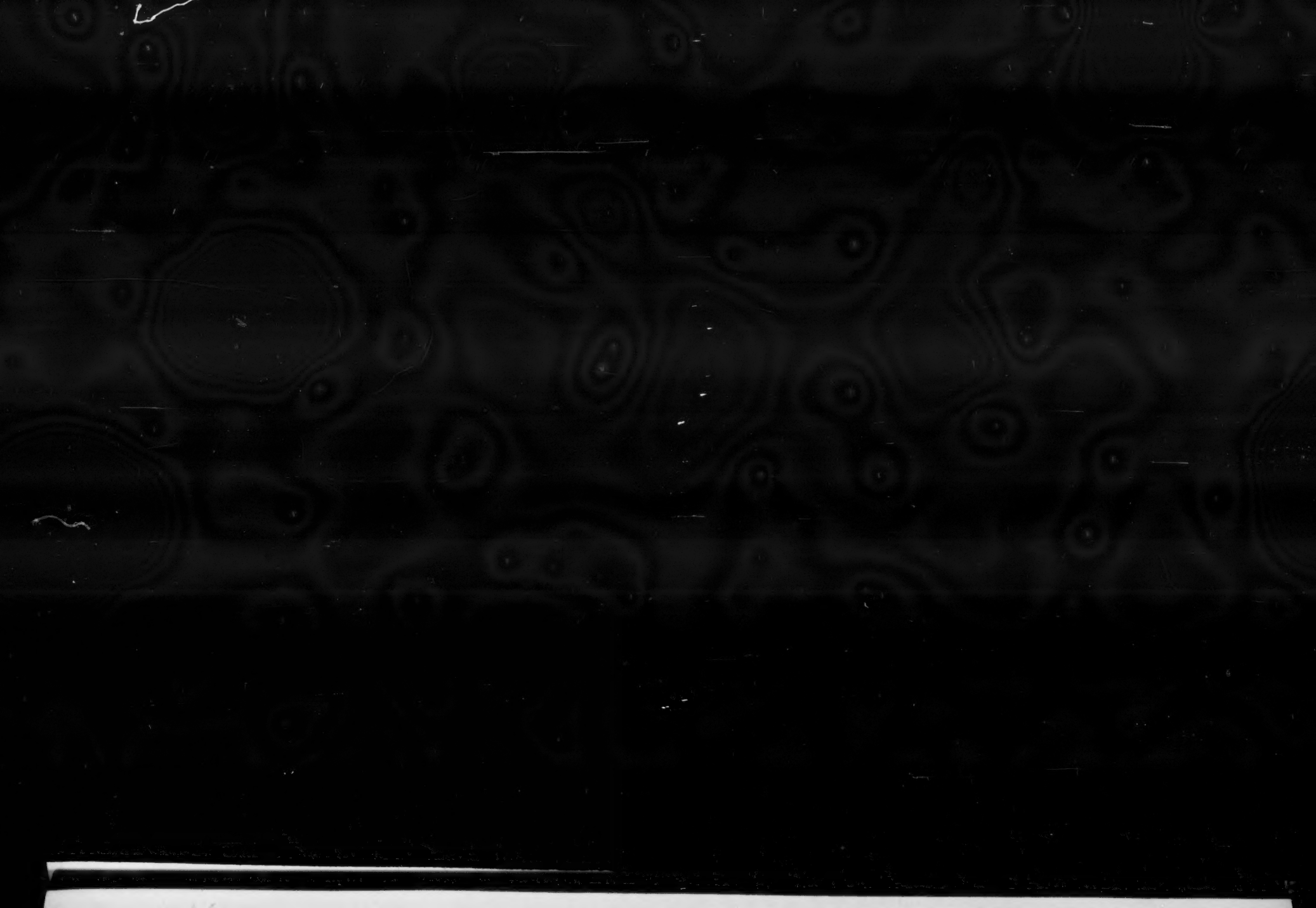
This book contains a great range of concentrated, worth-while information and should receive wide use as a textbook in our neighboring Spanish-speaking countries where there is a dearth of good medical textbooks in Spanish.

Announcement

Research on Orthopedic Appliances at Mellon Institute

Announcement has been made by Edward R. Weidlein, Director, Mellon Institute, Pittsburgh, Pa., of the establishment there of a comprehensive multiple research fellowship on orthopedic appliances by the Sarah Mellon Scaife Foundation of Pittsburgh. The program will be planned and carried out for the benefit of mankind through the medical profession.

Under the guidance of orthopedists and with the cooperation of leading organizations in the field as well as of manufacturers of orthopedic appliances, the fellowship will conduct broad scientific investigation and development relating to such appliances. Particular attention will be accorded to problems of mechanical design, improvements in materials of construction, and methods of fitting braces and similar orthopedic devices.

John L. Young, Ph.D., heads the program as Senior Fellow. A research specialist in metallurgy and mechanical engineering, he has been active on the investigatory staff of Mellon Institute since 1928. Eugene F. Murphy, M.E., Staff Engineer, Committee on Artificial Limbs, National Research Council, Washington, D. C., will serve as Advisory Fellow. Several research assistants will complete the initial personnel of the fellowship, whose adviser on the executive staff of the Institute is George H. Young, Assistant Director.

The medical advisory committee of the fellowship is under the chairmanship of Paul B. Steele, M.D., Professor and Head of the Department of Orthopedic Surgery, School of Medicine, University of Pittsburgh. The other members of this committee at the inception of the work are John A. Heberling, M.D., Associate Professor of Orthopedic Surgery, and Carl C. Yount, M.D., Assistant Professor of Orthopedic Surgery in the same institution.